Prevalence of Serological markers of Hepatitis B in patients with Inflammatory Bowel Disease

A dissertation submitted in part fulfillment of the requirements for DM (Gastroenterology) examination of the Tamil Nadu Dr. MGR Medical University, Chennai to be held in August 2015.

CERTIFICATE

This is to certify that this dissertation entitled Prevalence of Serological markers of Hepatitis B in patients with Inflammatory Bowel Disease is a bonafide work done by Dr. Patil Amol Prabhakar in partial fulfillment of the rules and regulations for D.M. (Gastroenterology) examination of Tamil Nadu Dr. MGR Medical University, to be held in August 2015.

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Dr. Amol Prabhakar Petal, Senior Registrar, Gastroenterology, Dr. Ebby George, Simon, Dr Sajith KG, Dr Ashish Goel, Gastroenterology, Dr. Anna B Pulimood, Pathology, Dr. Priya Abraham, Clinical Virology.

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CONTENTS

Introduction

IBD is a group of conditions which are idiopathic in origin producing chronic inflammation of the intestinal tract. Although IBD has been of considerable burden in the West, this entity is been increasingly diagnosed in Asian countries including India(1) This maybe due to increased awareness of the disease among physicians and improvements in the diagnostic modalities(1). Traditionally, mesalamine and steroid compounds have been used to manage IBD. More lately, immunomodulators and biological agents have been added to the therapeutic armamentarium.

Opportunistic infections including viral infections are observed in those with IBD, one of which is hepatitis B infection(2)Chronic hepatitis B infection which affects more than 350 million worldwide can result in cirrhosis and hepatocellular carcinoma(4).India is generally considered as an area of intermediate prevalence(3).Although an effective vaccine exists, its coverage in India is suboptimal thereby increasing the risk of transmissibility of the virus to vulnerable(2).IBD patients are at risk for hepatitis B infection when they are subject to blood transfusions and surgical intervention(4).With increasing use of immunosuppressive therapy in IBD, reactivation of the hepatitis B virus is possible(4)(5)(6).At the same time, data even from the West also show that hepatitis B vaccination coverage in those with IBD is low(7)(8)(9). The seroprotection offered by the immunization with standard dose of hepatitis B vaccine is also suboptimal (9)(10)(11).

Major guidelines on hepatitis B management strongly recommend testing for hepatitis B markers prior to initiating cytotoxic chemotherapy or highly immunosuppressive treatments(12)(13). ECCO guidelines advises treatment with for those positive for hepatitis B infection with anti viral starting two weeks prior to onset of immunosuppressive therapy till up to 6 months of

cessation of the same. On the other hand vaccination is recommended for all those who are seronegative .Unfortunately, the awareness regarding vaccination and hepatitis B infection in IBD patients has been dismal among gastroenterologists (7).

Data on the burden of hepatitis B infection in those with IBD is limited and the reported figures vary across studies (14)(15) . There has been no data in published literature from the Indian subcontinent with regard to this important issue and hence the need for embarking on this study.

AIM AND OBJECTIVES OF THE STUDY

Aim:

To study the prevalence of hepatitis B infection in patients with inflammatory bowel disease.

Objectives:

1. To study the prevalence of serological markers of hepatitis B exposure in patients with inflammatory bowel disease.
2. To study the hepatitis B vaccination status in patients with inflammatory bowel disease.

Review of literature:

Inflammatory bowel disease (IBD) comprises of three major disorders: ulcerative colitis, Crohn's and indeterminate colitis.

Ulcerative colitis:

Inflammation of the mucosal layer of the colon characterizes ulcerative colitis. It usually involves rectum and extends to proximal parts of colon in continuity.

Ulcerative colitis patients usually present with bloody diarrhea. As a result of rectal involvement stools are small and frequent in quantity. Colicky abdominal pain, urgency, tenesmus, and incontinence are associated symptoms. Patients who have distal involvement may have constipation as the only symptom. The severity ranges from mild disease with four or fewer stools with or without blood per day to severe disease with more than 10 stools per day (21). Fever, fatigue, and weight loss are also present. Symptoms secondary to anemia due to blood loss and anemia of chronic diseases include dyspnea and palpitation. The severity and presence of systemic symptoms depend on the clinical severity of the intestinal disease.

Crohn's disease:

Transmural inflammation and skip lesions are the characteristic lesion seen in Crohn’s disease (CD). The transmural inflammation may lead to fibrosis and strictures, and to obstructive clinical presentation. Transmural inflammation may also results in sinus tracts, giving rise to fistulae and perforation.

Abdominal pain is a common symptom of CD irrespective of the disease distribution. Transmural inflammation causes fibrotic strictures. Repeated episodes of small bowel and colonic obstruction are caused by these strictures. Right lower quadrant pain is frequently present in patients with disease limited to distal ileum. Patients will have no clinical manifestations of CD sometimes until luminal compromise causes constipation and signs of obstruction and abdominal pain. Manifestations like diarrhea, fistulas, malabsorption and bleeding, intraabdominal abscess are also seen in Crohn's disease. Extra intestinal manifestations like arthritis, uveitis, sacroileitis and skin manifestation like erythema nodosum, pyoderma gangranosum which may or may not be associated with disease activity are seen in both ulcerative colitis and CD.

Indeterminate colitis:

Surgical pathologists used the term "indeterminate colitis" for cases of severe colitis in which the resected colon showed features of both ulcerative colitis and Crohn's disease(16). The use of the term "indeterminate colitis" has widened to include colonoscopy and upper gastrointestinal (GI) endoscopic appearances, findings of video capsule endoscopy, biopsies, serology and radiology with each modality showing diagnostic features of both ulcerative colitis and Crohn's disease(17)(18). Indeterminate colitis is used in cases in which infectious causes are excluded and colonoscopy and upper GI endoscopy with biopsies, small bowel follow through or enteroclysis are not conclusive for Crohn's disease or ulcerative colitis(19). Postresection indeterminate colitis do have ulcerative colitis or Crohn's disease which was not diagnosed preoperatively(20).Indeterminate has been termed as temporary diagnosis as there is evolution to ulcerative colitis or Crohn's disease in some patients. Based on clinical, endoscopic and radiological features indeterminate colitis appears to be a distinct a subgroup among pediatric

patients(21)Few patients of indeterminate colitis have a phenotype of inflammatory bowel disease different from Crohn's disease and ulcerative colitis depends upon the identification of serological or genetic markers instead of the exclusionary criteria . At present indeterminate colitis remains a diagnosis of exclusion. Medical treatment trials of indeterminate colitis which are prospective are not reported. Until there is a generally accepted positive diagnostic test to use as an inclusion criterion a prospective randomized trial for medical treatment is unlikely. Few studies has shown benefit of Infliximab in medical refractory indeterminate colitis patients(22).Ileal-pouch anal anastomosis appears controversial in patients of indeterminate colitis with few medical centers showing similar results as in ulcerative colitis and few showing less favorable outcomes(23) (31). Since ulcerative colitis and Crohn's colitis both has an increased risk of colonic malignancy, it also appears that patients with prolonged course of indeterminate colitis may also have increased risk for colonic malignancy

Epidemiology:

The incidence of inflammatory bowel disease (IBD) changes accordingly as geographic location and ethnicity changes(24) .The areas with highest incidence are North America, England, North Europe and Australia. The incidence of IBD has been shown to be lower in southern compared with northern latitudes. In European countries and North America, incidence rates is 2.2 to 19.2 for ulcerative colitis and 3.1 to 20.2for Crohn’s disease(25)(26)(27). The incidence and prevalence of ulcerative colitis and Crohn’s disease seems to be lower in Asia and the Middle East(28). Seasonal variation in flares of IBD with peaks in the spring have been noticed(29) .

Temporal influence

IBD incidence may have changed over time. During the first several decades of the 20th century,the incidence of Crohn's disease was less than ulcerative colitis in America and northern Europe. The incidence of ulcerative colitis remained stable from the 1950s through the 1980s while an increase in incidence of Crohn's disease was persistently observed(30)(31). After that, the incidence of Crohn's disease seems to have plateaued and similar at present to ulcerative colitis in Europe and North America (32).The prevalence of ulcerative colitis has been reported to be substantially lower than among Europeans(33).

Ulcerative colitis can present at all ages .The diagnosis of ulcerative colitis below 5 years and above 75 years is not common. The peak incidence of ulcerative colitis occurs in 2nd and 3 rd decades of life and 2nd peak between 60-70 years. No gender difference is seen at all ages.

Crohn's disease is common in people in their 20s and teens, and also in people in their 50s through to their 70s. In childhood it is rarely diagnosed. Females children are affected more severely than male (34). Males are less likely to develop Crohn's disease than females. There is increased risk to develop disease in parents, siblings and children of Crohn's disease patients(35).

Risk factors for inflammatory bowel disease:

Age and gender: The age of onset is usually around 15 and 40 years. There is a bimodal age distribution for ulcerative colitis as well Crohn's disease with second peak seen between 50 to 80 years(36).

Racial and ethnicity :Ulcerative colitis and Crohn's disease are more common in Jews than non-Jews(37).Whites are affected more commonly than black and Hispanic populations (38).

Genetic susceptibility :10 to 25% IBD patients have a first degree relative with Crohn's disease or ulcerative colitis (39)(40).There appears to be concordance for the same disease type within families as with Crohn's disease(41).

Smoking: It has a variable effect on ulcerative colitis and Crohn's disease. Nicotine and smoking may directly smooth muscle tone, gut permeability, affect mucosal immune responses and microvasculature(42)(43)(44)(45).

Diet: Food antigens probably incite an immunologic response which results in IBD.Particular pathogenic antigens have not been identified yet. A diet with fried food, sugary foods, and processed food is associated with an increased risk of developing Crohn's disease and possibly ulcerative colitis. Cow's milk protein hypersensitivity has also been shown in infancy to cause of IBD(46). Sugar which is refined has been linked to the development of IBD(47)(48).Dietary fiber, from fruit, has been associated with a decrease in risk of Crohn's disease.(49)(50).

Physical activity :Physical activity has been associated with a decrease in risk of Crohn's disease(51).

Obesity :It is not clear whether obesity is associated with an increased risk IBD (52)(53).Accumulation of abdominal fat may lead to mucosal inflammation thereby altering the clinical course of established IBD(54).

Infections : Gut microbiome imbalance may lead to the development of IBD. The role of infections is suggested by the correlation between specific microorganisms and IBD and the association between acute gastroenteritis and IBD(55).

Nursing and other perinatal events: Breast feeding and perinatal events such as infections are implicated as a risk factors for IBD although the association is not clear(56)(57).

Antibiotics: Antibiotics, by altering the gut flora, may be a risk factor for IBD. Antibiotic use appears to have causal association(58)(59).

Oral contraceptives and hormone replacement therapy: Oral contraceptive and hormone replacement therapy through thrombotic effects may predispose to IBD. However the risk is small(60)(61).

Nonsteroidal anti-inflammatory drugs: NSAIDS can affect the interaction between immune cells in the intestine and the gut microbiome. They can also alter platelet aggregation, the release of inflammatory mediators, and micro vascular response to stress which are key events in the pathogenesis of IBD(62)(63).

Appendectomy: Appears protective for development of ulcerative colitis but the mechanism of is unknown(64)(65).

Psychosocial factors : The association is controversial and inconsistent(66)(67).

Etiology and pathogenesis:

The etiology of inflammatory bowel disease is multifactorial.It involves interaction of three elements.

1) Genetic susceptibility

2) Host immunity

3) Environmental factors

Genetics:

Genetics factors are risk factors for development of inflammatory bowel disease. Family history of IBD is one of the strongest risk factors. Animal and human studies have proved the association. IBD follows a non-Mendelian pattern of inheritance. Twin studies give the most compelling clinical evidence which suggest that genetic factors are more important in CD than in UC(68)(69). First-degree relatives have 3 to 20 times more risk to develop the disease than the general population (69). Sibling are diagnosed within ten years (70). Children of Jewish patients may be at a higher risk of developing IBD(71). Clinical features also demonstrate a heritable pattern. Concordance in the location (eg, ileal versus colonic) and type (eg, fibrostenotic, fistulas) of CD has been observed(72)(68).Genetic anticipation has also been described in inflammatory bowel disease(73)(74).It is been shown that the aggregate effect at several loci contributes to the IBD phenotype(75)(76). A genome-wide association studies (GWAS), have implicated 100 distinct susceptibility loci for IBD(77)(78)(79).

Intracellular innate immune pathways recognizing microbial products in the cytoplasm: The IBD1 gene on chromosome 16 encodes the protein NOD2 (CARD15). Mutations in IBD1 confer susceptibility to ileal CD(74)(80)(81).

The autophagy pathway : CD genes (ATG16L1, IRGM, and LRRK) regulate the autophagy pathway which is homeostatic process that enables recycling of intracellular organelles and contributes to the removal of intracellular microorganisms(79)(82). Some studies suggest NOD2 pathway regulate autophagy, integrated and defective in some patients with CD(83)(84).

Pathways regulating adaptive immunity: Genes regulating IL-17 and IL-23 receptor pathway have proposed as risk for IBD risk (eg, IL23R, IL12B, and STAT3). (STAT3, JAK2, and TYK2)genes overlap with the IL-10 pathway that has been associated with UC and CD(85).

Major histocompatibility complex: IBD with major histocompatibility complex (MHC) loci association has been proven multiple studies. HLA-DR2 is associated with UC, particularly in Japanese patients. Patients with HLA-A2, HLA-DR1, and DQw5 have increased risk of Extraintestinal manifestations of CD. In a GWAS of a Japanese population, HLA-Cw*1202-B*5201-DRB1*1502 haplotype is associated with increased chance of developing UC but decreased risk for CD(86).

CLINICAL MANIFESTATION OF ULVCERATIVE COLITIS:

Colitis: Ulcerative colitis patients present with chronic bloody diarrhea. It is usually a large bowel type diarrhea. Abdominal pain, urgency, tenesmus, and incontinence are usually associated.Patienst with distal disease can present with constipation. The onset of symptoms is usually insidious. The severity is from mild disease with four or fewer stools per day with or without blood and severe disease with more than 10 stools per day with continuous bleeding and severe cramps (87).Systemic symptoms including fever, fatigue, and weight loss are also reported. Symptoms of anemia are also noted. Physical examination is usually normal, especially in mild disease. Moderate and severe ulcerative colitis may have abdominal tenderness to, fever, pallor, hypotension and tachycardia. On rectal examination there may be blood. Physical examination may show muscle wasting, loss of subcutaneous fat, and peripheral edema due to malnutrition.

Disease severity: the severity is important for clinical management and assessing the long term prognosis. It is measured using a clinical disease activity index(88).

Mild: Patients have four or fewer stools per day which may or may not have blood without signs of systemic toxicity, and a normal ESR.

Moderate: Patients have frequent loose, bloody stools (>4 per day), mild anemia which does not require blood transfusions, and non-severe pain and minimal signs of systemic toxicity.

Severe – It is usually associated with frequent loos stools (≥6 per day) with blood and signs of systemic toxicity such as tachycardia (heart rate ≥90 beats/minute), fever (temperature ≥37.5ºC), anemia (hemoglobin <10.5 g/dL), and ESR (≥30 mm/hour).

Most of the ulcerative colitis patients present with mild disease , 27 percent of patients present with moderate disease, and 1 percent present with severe disease(89). The Mayo scoring system is used to assess disease severity and monitoring. Scores range from 0 to 12 with higher scores predicting severity(90).

Diagnosis: It is based on the history of diarrhea which persist more than four weeks and endoscopic and histologic features. Endoscopic and histological features are not specific for ulcerative colitis, so for confirming the diagnosis requires the exclusion of other causes of colitis.

LABORATORY FINDINGS: Patients with severe disease may have high ESR, electrolyte abnormality, low albumin and anemia. Patients with primary sclerosing cholangitis have raised alkaline phosphates. Stool studies include routine stool cultures and stool Clostridium difficile toxin, Giardia stool antigen and microscopy for ova and parasites .Serologic testing for sexually transmitted diseases including should be considered, particularly in patients with rectal symptoms.

Endoscopy and biopsy: In patients with ulcerative colitis endoscopic findings are nonspecific. The endoscopic features include erythematous appearance and loss of vascular markings due to engorgement of the mucosa and granularity of the mucosa, petechiae, exudates,

edema, erosions, touch friability, and spontaneous bleeding may present. Severe disease can be associated with ulcerations, profuse bleeding, and copious exudates. Pseudopolyps may be present.

Biopsy features suggestive of ulcerative colitis include architectural distortion such crypt abscesses, crypt branching, shortening and disarray. Epithelial changes such as mucin depletion and Paneth cell metaplasia may be seen. None of these features are specific for ulcerative colitis, the presence of two or more histologic features is suggestive of ulcerative colitis(91)(92).

In ulcerative colitis, rectum is usually involved initially which extends proximally in a continuous manner. In 30 to 50 percent of patients, disease is limited to rectum and sigmoid colon, 20 to 30 percent have left-sided colitis, and 20 percent of patients have pancolitis. Some patients have focal inflammation around the appendiceal not in continuity with disease elsewhere in the colon (a "cecal patch")(93)(94). Ileal inflammation (“backwash” ileitis) may occasionally be seen in patients with ulcerative colitis.

IMAGING:

Abdominal imaging is usually normal in mild to moderate disease patient, but may detect mucosal thickening or “thumb printing” due to edema. It can also detect colonic dilation in patients with severe ulcerative colitis.

Double contrast barium enema can be normal in mild disease. Barium enema shows diffusely reticulated pattern with punctuate collections of barium. In severe disease, it shows spiculated collar button ulcers, loss of haustrae, shortening of the colon, pseudo polyps, and filiform polyps and narrowing of the luminal caliber.

Ultrasound may show thickened hypoechoic mucosal layer in patients with active disease. Severe cases ma show transmural bowel wall thickening. Sonographic findings are non-specific for U.C and may be seen colitis due to other causes.

Computed tomography (CT) and magnetic resonance imaging (MRI) demonstrate thickening of the bowel wall which is nonspecific.

Clinical features of Crohn's disease:

Fever, abdominal pain, diarrhea with or without bleeding and weight loss are predominant symptoms of CD (95). Physical examination may be normal or may show pallor, weight loss. Other specific findings include perianal skin tags, sinus tracts, and abdominal tenderness.

Abdominal pain: Abdominal pain is a commonest feature .Transmural involvement causes fibrotic strictures leading to repeated episodes of small bowel and colonic obstruction. Patient whose disease is limited to the distal ileum may presents with pain right lower quadrant.

Diarrhea: Diarrhea is a common presentation. A history of chronic diarrhea without bleeding but with extra intestinal manifestations of (IBD) (eg, skin, eye, or joint problems) suggests the diagnosis of CD. Diarrhea associated with CD may result from secretion of excessive fluid and impaired fluid absorption by inflamed small or large bowel, malabsorption of bile salt and steatorrhea.

Bleeding: There may occult gastrointestinal blood loss and overt bleeding is less common however patients with Crohn's colitis can have overt bleeding.

Fistulas -Transmural inflammation is associated with the development of fistulas. It is usually an indolent process. Fistulas connect two epithelial-lined organs. Common types for fistulas are enterovesical, enterocutaneous, enteroenteric and enterovaginal.

Phlegmon/abscess: Sinus tract do not from fistulas every time. They may present as a phlegmon which may be palpable on physical examination. Mass in the right lower quadrant may suggest ileal involvement. Abscess may form in sinus tracts which lead to localized peritonitis with fever, abdominal pain and tenderness

Perianal disease: Perianal disease may occur in more than third of patients with CD and may cause symptoms like perianal pain and discharge from large skin tags, perirectal abscesses, anal fissures and anorectal fistulas.

Malabsorption: Occurs due to bile salt diarrhea as the terminal ileum is commonly involved. Steatorrhea may also result from bacterial overgrowth from enterocolonic fistulas, small bowel stricture or extensive disease. Steatorrhea can lead to severe malnutrition and manifestation of fat soluble vitamin deficiency.

Other gastrointestinal involvement.: There may be frequent apthous oral ulcers .Esophageal CD can present as dysphagia.Gastroduodenal CD can be seen in 15 percent of patients, may present as of gastric outlet obstruction or upper abdominal pain (96). Gallstones are also seen commonly (97).

Extraintestinal manifestation of inflammatory bowel disease:

IBD is associated with multiple extraintestinal manifesations. Ten percent of patients with IBD usually develop extraintestinal manifestations initially. However 25 percent of patients develop extraintestinal manifestations in the course of the disease(98). EIM usually follow the clinical course of IBD except primary sclerosing cholangitis and ankylosing spondylitis.

Musculoskeletal: The most common extraintestinal manifestation of IBD is arthritis. IBD is associated with peripheral arthritis which usually involves large and small joints and ankylosing spondylitis. Osteopenia, osteoporosis and osteonecrosis are other manifestations of IBD.

Arthritis can affects appendicular joints, the spine, sacroiliac joints or a combination of these joints. Peripheral arthritis can be remitting and acute in onset when it is called Type I arthropathy or it can be chronic and have frequent relapses when it is called type 2 arthropathy(99).IBD complications can cause joint pain that should be distinguished from sterile inflammation. Bacterial infection of the peripheral and sacroiliac joint can occur due to fistulization and bacteremia. Joints can also be affected due to adverse effects of IBD treatment. Osteonecrosis due to glucocorticoids use is common.

Spondylitis can occur up to 26 percent IBD patients (100)(101) Females are less commonly affected than males. Prolonged stiffness in the back in the morning or after rest is the usual symptom. Exercise relives pain and stiffness usually. Symptoms are not related to the gastrointestinal disease. Asymptomatic sacroileitis by radiological detection is seen up to 18 percent of patients with IBD(102).There is no increased frequency of HLA-B27 in patients with IBD and sacroileitis.

Type I arthropathy — It is acute, affects six or fewer joints and is associated with flares of the bowel disease usually in initial stages of the disease. It is self-limiting and does not cause joint deformities. The knee is most commonly affected. Five percent of IBD patients develop type I arthropathy. Joint symptoms can arise prior to the onset IBD.

Type II arthropathy — It is a polyarticular disease with metatarsophalangeal joints being commonly involved (99). Other joints like proximal interphalangeal, metatarsophalangeal joints, ankles, knees, shoulders elbows and wrists joint are infrequently involved. Approximately one-half of the patients with IBD have migratory arthritis. Synovitis which is active can remain for months and can relapse multiple times. Exacerbations and remissions of the symptoms can persist for years. It affects up to 4 percent of IBD patients. Joint involvement infrequently can occur before the diagnosis of IBD and joint symptoms do not follow the activity of bowel disease(99).

Skin:

Erythema nodosum — This skin disorder is frequently seen with ulcerative colitis and Crohn's disease and can occur in 4 percent of patients(103). It occurs as raised, tender, red subcutaneous nodules. The size can vary from 1 to 5 cm. Extensor surfaces of the extremities are the usual location of the nodules specifically over the anterior tibial area. Biopsy from these lesions shows focal panniculitis. The diagnosis is most often clinical and biopsy is rarely required.

Pyoderma gangranosum — Very few patients of inflammatory bowel disease develop pyoderma gangranosum (104) . It usually affects only 0.75 percent of patients (103).It is relatively infrequent, however it has more serious consequences than other skin disease associated with IBD such as persistence and local discomfort even after appropriate therapy.

It usually occurs as single or multiple erythematous papules or pustules. It shows pathergy as lesions which are usually preceded by trauma to the skin. The most common locations are the legs, but it may develop in other parts of the body such the abdominal wall adjacent to the stoma after colostomy as well as in areas of trauma or other surgical scars (105). Deep ulcerations develop due to necrosis of dermis which is sterile on culture. Biopsy reveals findings such as sterile abscess.

Pyoderma gangranosum parallel IBD activity in half of the cases(106). Therapy of underlying IBD results in healing although treatment often includes a long course of high dose glucocorticoids.

Eye – Common ocular manifestations of IBD include episcleritis and uveitis, scleritis, iritis , and conjunctivitis. It can be asymptomatic or patients may complain of burning, itching or redness of the eyes.

Episcleritis/Scleritis It occurs in up to 5 percent of patients with IBD(107).Patients may be asymptomatic or complain of itching and burning ciliary vessels injection and inflammation episcleral tissues are important features on examination.Episcleral nodules can also be seen.

Uveitis — This is less common than other eye conditions associated with IBD and occurs up to 3 percent of patients with IBD. The consequences are more severe with uveitis. It is bilateral, insidious in onset ,posterior to the lens, chronic and is more common in females than males(108). It is usually associated with arthritis in 75 percent of patients which may be axial and/or peripheral and therefore seems like spondyloarthropathy. It may be difficult to differentiate between these disorders as half of patients with IBD have the HLA-B27 phenotype .(109)The common symptoms are blurred vision, eye pain, photophobia, and headaches. A slit-lamp examination shows inflammation in anterior chamber with per limbic edema, cells, and protein. Conjunctival injection and corneal clouding can also be seen. Iris atrophy, lens deposits, and synechiae can develop after an acute episode.

Hepatobiliary: Primary sclerosing cholangitis and autoimmune liver disease are usually associated with IBD. Primary sclerosing cholangitis patients are usually asymptomatic and are suspected due to elevation in the alkaline phosphates concentration. Common symptoms are right upper quadrant pain, fevers, fatigue, pruritus, chills and night sweats.

Hematopoietic: IBD patients are at an increased risk for venous and arterial thromboembolic events.(110)(111)

Diagnosis:

Laboratory findings: There may be anemia, vitamin B12 deficiency and raised inflammatory markers such as ESR and CRP. In cases of diarrhea, a stool specimen should be examined for culture, ova and parasites and C. difficile toxin.

Endoscopy:

Colonoscopy — Colonoscopy with ileal inspection is the modality of choice for diagnosis. Endoscopy shows ulcerations near the normal appearing mucosa with polyploidy mucosal changes which give rise to cobblestone appearance. CD involvement is typically focal with normal appearing bowel segments in-between. Pseudopolyps are also often present. Rectal sparing is common in Crohn's disease. Biopsies are obtained from the right colon, left colon, and rectum even if endoscopically normal in appearance to assess for microscopic inflammation.

The major findings on intestinal biopsy are focal ulcerations, acute and chronic inflammation. These findings are usually confirmatory rather than diagnostic. Granulomas are seen up to 30 percent of CD patients and are diagnostic.

Wireless capsule endoscopy — Wireless capsule endoscopy is being used frequently for the evaluation of suspected and established small bowel Crohn disease. It provides another way

of small bowel visualization. It can detect lesions which are suggestive of CD but not visible by other studies.

Imaging studies — They are useful to evaluate the upper gastrointestinal tract and for detection of the length and location of strictures in areas not accessible by colonoscopy. Imaging studies includes barium studies, such as barium enema or upper gastrointestinal series with small bowel follow through (SBFT), computed tomography (CT) and magnetic resonance (MR) enterography in patients with Crohn disease.

Medical management of ulcerative colitis:

Management depends upon disease location and severity.

Ulcerative proctitis or proctosigmoiditis:

Topical 5-aminosalicylic acid (5-ASA) medications are first-line treatment. 5-ASA suppositories and enemas induce remission in more than 90 percent of patients with mild to moderate proctitis(112)(113). Topical therapies are quicker to act than oral preparations and require less dosing(114).Patients reluctant or who are unable to tolerate topical medications are treated with oral 5-ASA medications. Oral therapy alone is effective in the induction of remission in patients with proctitis and proctosigmoiditis in but response rate is lower than topical therapy (115).Patients who do not have response adequately to topical therapy are usually treated with the combination of oral 5-ASA and topical 5-ASA enemas or

suppositories(115). For patients who do not respond to topical 5-ASA medications in four to six weeks, a combination of topical 5-ASA and topical steroids should be used(116).

Maintenance therapy: For patients with first episode of mild ulcerative proctitis who have responded to treatment, maintenance therapy is not recommended. Many such patients continue to be in remission for long periods without having a relapse and even if it occurs, the response to therapy is often prompt and complete. Patients with ulcerative proctitis who have more than one relapse in a year and in all patients with proctosigmoiditis, maintenance therapy is recommended (117).

Left-sided colitis, extensive colitis and pancolitis:

Combination therapy with oral 5-ASA medications, 5-ASA or steroid suppositories, and 5-ASA or steroid enemas or foam are beneficial in patients with mildly or moderately active left-sided colitis and pancolitis(118). Oral glucocorticoids are effective in inducing remission in patients with active ulcerative colitis in patients non-responsive to 5-ASA and tropical therapy(119).

Maintenance therapy: In all patients with left-sided colitis, pancolitis, or extensive colitis; maintenance therapy is recommended.

Steroid refractory ulcerative colitis: Patients without clinical response to glucocorticoids in doses of prednisone upto 40 to 60 mg/day within 30 days for oral therapy or 7 to 10 days for intravenous therapy are considered to have steroid-refractory disease. Medical therapy with cyclosporine as a "bridge" to therapy with longer acting medications azathiporine and

Mercptopurine and an anti-tumor necrosis factor (anti-TNF) agent, additional are considered for patients with steroid-refractory ulcerative colitis.

Steroid dependant ulcerative colitis:

Steroid dependence is defined as where glucocorticoids cannot be tapered to less than 10 mg/day within three months of starting steroids without recurrent disease, or where relapse occurs within three months of stopping glucocorticoids. Longer acting medications like Azathioprine and Mercptopurine and Anti-TNF agents are options for steroid dependant patients.

Medical management of Crohn's disease:

Usually disease severity dictates management. The Crohn's Disease Activity Index (CDAI) and similar scoring systems are used to assess the disease activity in crohn's disease(120). The latter have been shown to correlate with the CDAI(121). A drop in the CDAI of 100 points corresponds to a 3-point drop in the HBI. A CDAI of <150 (clinical remission) corresponds to Harvey-Bradshaw Index of <4.

Disease severity according to CDAI is defined as follows

Asymptomatic remission (CDAI <150): Defined as patients who have remission either spontaneously or after medical or surgical therapy. Patients who require steroids to remain asymptomatic are not in remission and are labeled as steroid-dependent.

Mild to moderate Crohn disease (CDAI 150-220) – Refers to patients who are tolerating an oral diet without dehydration, mass, obstruction, toxicity, abdominal tenderness or >10 percent weight loss.

Moderate to severe Crohn disease (CDAI 220-450) – Patients who did not respond to management for mild to moderate disease and patients with weight loss, fever, nausea ,vomiting, abdominal pain and tenderness or anemia.

Severe-fulminant disease (CDAI >450):Persisting symptoms such as high fevers, intestinal obstruction, persistent vomiting, cachexia, significant peritoneal signs or an abscess despite glucocorticoids or biologic agents (Infliximab, adalimumab, certolizumab pegol or natalizumab).

Drugs used in management of mild to moderately severe Crohn's disease:

5-ASA drugs — There is controversy regarding the use of 5-ASA drugs for Crohn's disease. Studies have produced mixed results evaluating the efficacy of 5-ASA drugs in Crohn's disease. Meta-analysis have shown that Mesalamine is not superior to placebo in induction and maintenance of remissions but some studies have shown that Sulfaslazine is superior to placebo but inferior to steroids in inducing remission. Higher dose of mesalamine (1.5gm/day) is also shown to induce remission in Crohn's disease(122).

Glucocorticoids — For mild to moderate disease, oral glucocorticoids continue to be the mainstay of treatment and for those presenting with more severe symptoms but not requiring intravenous glucocorticoids and hospitalization (123)(124)(125). Antibiotics and 5-ASA drugs

can be used concomitantly with prednisone. Because of significant side effects, glucocorticoids should not be used long-term.

Non-systemic glucocorticoids — For the induction of remission in active ileitis or right-sided colitis among patients who did not tolerate or who have contraindications to systemic glucocorticoids. Controlled ileal release budesonide which has high first-pass hepatic metabolism can be used as a prednisone alternative. Systemic side effects are less common with budesonide than with conventional glucocorticoids. It cannot be used for maintenance of remission although budesonide is recommended as first-line therapy for mildly to moderately active Crohn's disease(116).

Antibiotics: In septic complication of IBD such as wound infections and abscesses, antibiotics have very effective role in the treatment. Although they are not an established treatment of the primary disease processes of Crohn's disease, ulcerative colitis, they are still used commonly(126)(127)(128).Antibiotics may also act as immunomodulators and exert their beneficial effects apart from antimicrobial effects(129)(130).

Drugs used in management of severe and refractory disease:

Azathioprine and 6-mercaptopurine: Azathioprine and its active metabolite, 6-mercaptopurine are used in patients with refractory Crohn's disease. The response rate is 60 to 70 percent in both small bowel and colonic disease. Three to six months are required to notice

response to these medications. Patients usually require concomitant steroid therapy with a tapered steroid dose after one to two months of treatment with these agents.

Methotrexate —For patients who show intolerance or do not respond to Azathioprine or 6-MP; methotrexate is an alternative and may be preferable to Azathioprine or 6-MP in patients with arthropathy associated with CD. A response is usually seen within three months.

Biologic therapies:

Anti-TNF therapies — Three anti-tumor necrosis factor therapies are approved for treatment of luminal Crohn's disease in adults and they all are effective. Patients who are unlikely to benefit are those with fibrostenotic Crohn's disease without active inflammation. Patients who are intolerant to one anti-TNF agent may tolerate a different agent. In moderately active, steroid refractory Crohn disease, Infliximab has been shown to be useful for induction of remission after initial infusion and for maintenance of remission for up to 54 weeks. Its use has been associated with reduction in the risk of hospitalization and surgery along with improved quality of life(131).

Hepatitis B:

Even after the availability of an effective vaccine for Hepatitis B virus, infection remains a global health issue. In the world, there are up to two billion individuals with evidence of hepatitis B infection. Of these, 400 million are chronic carriers and 500,000 to 1.2 million will succumb very year to cirrhosis and hepatocellular carcinoma.

Epidemiology— In areas with low prevalence like United States and Canada, Western Europe, Australia; the prevalence of HBV carriers varies from 0.1 to 2 %. In intermediate prevalence areas like Mediterranean countries, Japan, Central Asia, Middle East, and South America; it is around 3 to 5 percent while in areas with high prevalence like southeast Asia, China, sub-Saharan Africa; the prevalence is around 10 to 20 percent (132)(133).The variation in HBV carrier rate in different geographical regions of the world is because of differences in the age of acquisition of infection. For vertically transmitted infection; the rate of progression to chronic HBV infection is around 90 percent (134), between the age of 1 and 5 years the risk is 20 to 50 percent (135) and for adult acquired infection, the risk is less than 5 percent. In India, the estimated hepatitis B virus carrier rate in India is 4% with a total of around 36 million carriers(136).

Mode of transmission: The mode of transmission varies according to the geographical area. In high prevalence areas, vertical transmission causing perinatal infection is the most common mode of transmission (133)(137). In intermediate prevalence areas, horizontal transmission in childhood, accounts for most common cause of chronic HBV infection. Intravenous drug use and

unprotected sexual intercourse are the major routes of transmission in low prevalence areas in adults.

Screening for hepatitis B virus is performed by testing for HBsAg. Negative patients should be vaccinated.

The following groups should be screened for HBV infection(12).

1. Adolescents, who engage in high-risk behaviors like unprotected sex with an infected partner or more than one partner, use of intravenous or intranasal drugs, those with a history of sexually transmitted disease and men having sex with men.
2. All internationally adopted children.
3. Immigrants from high prevalence areas (regions in which the HBsAg prevalence is more than 2 percent).
4. Children who are living in communities where HBV is endemic.
5. Household contacts of individuals with HBV infection.
6. Infants born to women with HBV infection.

Clinical manifestation:

Acute HBV infection: The diagnosis is established in those who are positive for HBsAg IgM anti-HBc. One to four months is the incubation usually. A serum sickness-like syndrome usually develops in the prodromal period which is followed by constitutional symptoms such as right-upper-quadrant discomfort, jaundice, anorexia and nausea. After one to three months the symptoms and jaundice generally disappear. Subclinical or anicteric hepatitis develops in

around 70 percent of patients with acute hepatitis B and another 30 percent develop icteric hepatitis. The disease is usually more severe in patients who have confection with other hepatic viruses(138). In approximately 0.1 to 0.5 percent of patients, fulminant hepatic failure develops which is unusual(139).The age at infection decides rate of progression from acute to chronic hepatitis B (134). The rate is around 90 percent for vertically acquired infection. For infections between the age of one and five years, the rate is 20 to 50 percent and less than 5 percent for an adult-acquired infection(135) (137).

Treatment: Acute hepatitis B treatment is supportive. Exposed contacts should be prevented from infection with appropriate measures. The role of nucleoside/tide therapy is not clear at present.

Chronic HBV infection: HBsAg persistence for more than 6 months satisfies the criteria for chronicity. In chronic infection IgG anti-HBc is positive, while IgM anti-HBc is negative. Most of the patients are asymptomatic while some patients may have fatigue. Exacerbations of the infection which may be asymptomatic can mimic as acute hepatitis or manifest as hepatic failure.

Chronic Hepatitis B infection can have different phases. The interplay between virus multiplication and the immune response of the host decides the natural course of chronic hepatitis B virus infection. There are two phases of chronic HBV infection usually: an early replicative phase with active liver disease and a phase with low replication and remission of liver disease(140)(141). In vertically acquired HBV infection, virus replication is not accompanied by active liver disease. This is called as immune tolerance phase(142).

Replicative phase:

Immune tolerance — In vertically acquired HBV infection, the early phase is characterized by high HBV replication. There is the presence of HBeAg and high levels of HBV DNA in serum, however there is no evidence of liver disease as there are no symptoms, normal serum liver enzymes concentrations and minimal changes on liver biopsy(143)(144).

Immune clearance: In the second and third decades in patients with vertically acquired HBV infection, transition from the immune tolerance to the immune clearance phase occurs. The annual rate of spontaneous HBeAg clearance increases to 10 to 20 percent during the immune clearance phase(145)(146).HBeAg seroconversion is sometimes accompanied by biochemical exacerbations(147)(148). Most of the exacerbations develop without symptoms and usually identified during routine follow-up. In some patients, symptoms of acute hepatitis develop and may erroneously lead to diagnosis of acute hepatitis B (149).

Low or nonreplication phase/inactive carrier state: Low or nonreplicating phase/inactive carrier state patients are those who are HBeAg negative and anti-HBe positive. Even when tested by PCR assays, HBV DNA is undetectable in serum in some patient. Liver disease is in remission as there is no evidence of necroinflammation in liver biopsies and normal liver function test.

HBeAg-negative chronic hepatitis : Some patients remain HBeAg negative however they develop moderate levels of HBV replication and active liver disease (elevated liver function test and liver biopsy showing chronic inflammation)(150)(151). Such patients are

said to have HBeAg-negative chronic hepatitis. Due to precore or core promoter genetic variations, they cannot produce HBeAg and have a residual wild-type virus or HBV variants(152)(153).HBeAg-negative chronic hepatitis patients are older and they can have advanced liver disease and have fluctuations in HBV DNA and liver enzymes.

Resolution of chronic HBV infection: Patients with chronic HBV infection become HBsAg negative sometimes. The annual rate of clearance of HBsAg is usually around 0.5 to 2% in Western countries and around 0.1 to 0.8% in Asian countries(154)(155).Clearance of HBsAg does not safeguard from the development of hepatocellular carcinoma or cirrhosis although they have a favorable prognosis(156).

Sequelae of chronic Hepatitis B infection: Inactive carrier state to the development of cirrhosis, hepatocellular carcinoma, hepatic decompensation, extrahepatic manifestations and death are the usual sequel of hepatitis B infection.

Chronic Liver Disease: Chronic Hepatitis B progresses to compensated and decompensated chronic liver disease at different rates(157).

- Chronic hepatitis to cirrhosis develops in around 12 to 20 %
- Compensated cirrhosis to hepatic decompensation develops in around 20 to 23 %
- Compensated cirrhosis to hepatocellular carcinoma develops in around 6 to 15 %.

Hepatocellular carcinoma : Seen in both Asian and Western populations. Hepatocellular carcinoma (HCC) is described in children and adults with HBV infection(158)(159). In perinatally acquired HBV infection, HCC develops at a rate of about 5 percent per decade. The risk is related to the degree of histologic injury, the duration of disease, HBV DNA levels. HBeAg positive patients and those with precore mutants have higher risk.

Treatment of Hepatitis B:

Treatment of chronic HBV is shown to decrease the risk transmission to others, progressive CLD and other long-term complication such as hepatocellular carcinoma.

Patients can be categorized for treatment as follows: (160)

Patients in whom therapy is definitely indicated:

- Clinical complications of chronic liver disease
- Prevention of reactivation of chronic HBV during chemotherapy and immunosuppresion
- Cirrhosis and advanced fibrosis associated with high serum HBV DNA.

Therapy may be indicated in following group of patients:

- Those with immune-active phase.

Immediate therapy is not routinely indicated in following groups of patients

- Immune tolerant phase.
- Inactive carrier phase.
- Latent HBV infection (HBV DNA without HBsAg).

Recommendations from the EASL suggest that patients with HBV DNA levels greater than 2000 IU/mL, having serum ALT levels above the upper limit of normal (ULN) with evidence of moderate to severe necroinflammation and/or at least moderate fibrosis on liver biopsy should be treated(13).

HBeAg-positive patients:

In patients with HBV DNA >20,000 IU/mL and ALT >2 x ULN; anti-viral therapy is recommended. Those having cirrhosis which is compensated and HBV DNA >2000 IU/mL and those with decompensated cirrhosis and detectable HBV DNA by PCR assay should be treated. Observation can be done in patients with chronic hepatitis with serum ALT less than two times the normal but should be considered for treatment when the serum ALT becomes elevated. Patients who have icteric flares, recurrent hepatitis flares that fail to clear HBeAg, those with active or advanced histologic findings, and patients older than 40 who remain HBeAg positive and with high HBV DNA levels are exceptions.

HBeAg-negative patients:

Treatment may be initiated when serum ALT is more than two times the normal and HBV DNA is more than 2000 IU/mL as sustained remission is rarity without treatment. Follow-up is required to differentiate an inactive carrier state from HBeAg negative chronic hepatitis because HBeAg negative chronic hepatitis has a fluctuating course. In HBeAg negative patients who

have serum HBV DNA levels >2000 IU/mL and normal or mildly elevated ALT, a liver biopsy should be considered to determine if therapy is required.

Treatment:

Therapy for chronic HBV includes Interferon, Lamivudine, Adefovir dipivoxil, Telbivudine, Entecavir and Tenofovir.

Interferon: The advantages are the absence of selection of resistant mutants, finite duration of treatment and more durable response. Interferon side effects can be troublesome for some patients and severe side effects are less common. Interferon is contraindicated in patients with decompensated disease. The main role of interferon is in treatment of young patients with well compensated CLD who do not want long-term treatment or are planning family.

Lamivudine: Advantages of Lamivudine are its lower cost, the many years of experience and its safety as it appears safe during pregnancy. The high rate of drug resistance is the main disadvantage of Lamivudine.

Adefovir: Advantage of Adefovir is its activity against Lamivudine-resistant HBV and a lower rate of drug resistance compared to Lamivudine.

Entecavir: Its potent antiviral activity is the main advantage along with a lower rate of drug resistance. Entecavir has a more important role in primary treatment of HBV than in patients

with Lamivudine resistant HBV. It has important role in patients with decompensated cirrhosis because of its potent antiviral activity and low rate of drug resistance.

Tenofovir: Has more potent antiviral activity than Adefovir and is effective in suppressing wild-type as well as Lamivudine-resistant HBV. In treatment-naïve patients, Tenofovir may be used as first line treatment and in patients with Lamivudine, Telbivudine or Entecavir resistance.

Immunosuppresion and Hepatitis B:

Interplay between viral multiplication and the host's immune response determines the natural course of HBV infection. In patients with evidence of serological recovery, HBV persists in the body. Individuals who receive immunosuppressive therapy are at risk for HBV reactivation and a flare of their HBV disease. Reactivation can result in increased serum liver enzymes, hepatic failure, or death(161). Reactivation leads to an interruption of immunosuppressive therapy causing delay in the treatment of the underlying disease.

Patients at risk of Hepatitis B activation:

1) **Chemotherapy:** Patients receiving chemotherapy for hematological and solid malignancy(162)(163)(164).

2**) Autoimmune disease** : Autoimmune diseases patients treated with immunosuppressive therapy are at risk of reactivation(6)

3) **Transplantation**: Patients who have received stem cell or solid organ transplantation and on immunosuppresion are at risk for Hepatitis B reactivation.

The risk depends on Immunosuppresion received and on HBsAG status. Individuals who are HBsAg-positive are at greater risk for HBV reactivation than those who are HBsAg-negative. HBsAg-positive individuals who are HBeAg positive with high HBV DNA have highest risk(162)(163). HBsAg-negative, anti-HBc-positive patients are also at risk for reactivation with immunosuppressive therapy. Reactivation can occur in anti-HBs-positive patients. Patients who have detectable anti-HBs have a lower risk of HBV reactivation, however titers can decrease to undetectable levels during immunosuppressive therapy.

The immunosuppressive agent determines the risk for HBV reactivation. The number of drugs that are associated with reactivation are constantly increasing, such as glucocorticoids, traditional chemotherapeutic agents and biologic agents (anti-CD 20 agents, anti-TNF agents) and new classes of drugs such as mechanistic target of rapamycin (mTOR)-inhibitors and tyrosine kinase inhibitors

Glucocorticoids :HBV reactivation occurs with high-dose and rapidly tapered regimens and moderate-dose, prolonged regimens. Reactivation has not been frequently described with low-dose regimens (<20 mg or prednisone per day) even over prolonged periods(165). Glucocorticoids increases HBV replication. The enhanced viral replication is because of glucocorticoids responsive element in the HBV genome that increases transcriptional activity(166). Serum aminotransferase tend to decrease inspite of the increase in viral replication. The reverse occurs once glucocorticoids are tapered, viral replication decreases and

aminotransferases increase(167)(168). It usually takes four to six weeks after withdrawal to cause peak rise in aminotransferase (169).

TNF alpha-inhibitors: HBV reactivation has also been associated with TNF alpha inhibitors among those with Crohn's disease and psoriasis. Reactivation can occur in both who are HBsAg-positive as well negative. Reactivation rates have been lower in HBsAg-negative individuals than those observed with rituximab (165).

Anti-CD 20 agents : FDA has issued warnings for the monoclonal anti-CD20 antibodies atumumab and rituximab for an increased risk of reactivation among patients positive for HBsAg or anti-HBc(170)(171)(172)(173).

Stratifying risk of Hepatitis B activation:

The AGA and the AASLD have categorized the level of risk for HBV reactivation based on type of immunosuppressant used and patients serological status(165). The level of risk determines whether or not preventive therapy is needed.

Risk is stratified as follows

Very high-risk: Those who are HBsAg-positive and are going to undergo hematopoietic stem cell transplantation and/or receive anti-CD20 therapy (eg, rituximab).

Moderate-risk: Patients receiving cytotoxic chemotherapy without glucocorticoids and patients going to receive anti-TNF therapy or anti-rejection therapy for solid organ transplants are at moderate risk of reactivation in HBsAg positive individuals. Patients

who are HBsAg-negative and anti-HBc positive are at moderate risk for reactivation if they are going to undergo hematopoietic stem cell transplantation or going to receive anti-CD20 therapy (eg, rituximab or ofatumumab).

Low-risk: HBsAg-positive patients receiving methotrexate or azathiporine are at low risk of reactivation. HBsAg-negative individuals are also at low risk if they are receiving cytokine inhibitors (eg, anti-CD52 agents) or high-dose glucocorticoids (eg, ≥20 mg/day)

Very low-risk : Patients receiving anti-TNF therapy, cytotoxic chemotherapy without glucocorticoids or anti-rejection therapy for solid organ transplants; HBV reactivation occurs rarely in HBsAg-negative patients.

Clinical manifestation of reactivation of Hepatitis B:

Reactivation is asymptomatic most of the times or some patients develop increase in HBV DNA levels or in transaminase levels. Some patients may also develop acute hepatitis, hepatic failure or hepatic decomposition or death can also occur in some patients. Underlying cirrhotic patients have worse outcomes.

Diagnosis:

Diagnosis of reactivation is made when there is increase in HBV DNA level.

HBV reactivation is diagnosed when with serological evidence of HBV patients have:

1) A detectable HBV DNA level without previous evidence of virus.

2) A rise in HBV DNA of more than 2 $\log_{10}$IU/mL in patients who had HBV DNA present at baseline. HBV reactivation is defined as more than tenfold increase in HBV DNA compared with baseline in some studies(174).

Treatment of HBV reactivation:

Anti-virals should be administered to all who develop reactivation. Renal functions dictate the choice of anti-virals as Tenofovir is contraindicated in patients with renal dysfunction. The aim of the therapy is to prevent flare of disease and to avoid decompensation. Lamivudive has low barrier to resistance so Tenofovir and Entecavir is preferred.

Treatment to prevent reactivation:

In moderate to high risk patients, anti-viral therapy should be initiated. Antiviral therapy started after the onset of reactivation may not prevent a flare (175)(176)(177)(178).Monitoring should be done in low risk patient and treated upon detection of flare. The choice of anti-virals is similar to as for treatment of flare. Type of immunosuppressive therapy, the degree of underlying liver disease and baseline HBV DNA level decides the period of therapy for treatment and prevention which is similar. Post Immunosuppresion treatment should be continued for at least 6 months. Treatment should be continued for 12 months post Anti-CD 20 therapy as there is a lag in recovery in function of B cells. In patients who have undergone solid organ transplantation or hematopoietic stem cell, antiviral therapy may need to be continued long-term since they remain on long term immunosuppressive medications. In addition, certain HBsAg-positive patients (eg, those with a baseline HBV DNA >2000 IU/mL or evidence of cirrhosis) may need prolonged treatment.

Hepatitis B and inflammatory bowel disease.

Inflammatory bowel disease (IBD) treatment is improved by the increasing use of immunosuppressors and use of biological. Immunomodulators are used more early and frequently in the course of disease as there is a substantial evidence for them. Many issues regarding relationship between Hepatitis B and IBD remained unresolved like prevalence of Hepatitis B and the target population in whom screening should be done(15). Natural history of Hepatitis B is clearly impacted by Immunosuppresion, however it is unclear which factors increases the reactivation of Hepatitis B on Immunosuppresion. It is also unclear regarding which patients need anti-viral prophylaxis and choice of anti-viral. There is a consensus for the use of Hepatitis B vaccination among inflammatory bowel disease however it is underused in practice.HBV vaccination efficacy in IBD patients and the factors modifying its efficacy are unknown(179). Modified vaccination scheduled can be used and is suggested to increase the efficacy rate in patients of inflammatory bowel disease. Anti-HBsAg titer testing is suggested after vaccination however the cut-off values for optimal response are controversial(180). Second course of vaccination is suggested after the first course fails however efficacy of the second course is not proven.

Prevalence of Hepatitis B in inflammatory bowel disease.

Although not much information is available regarding the prevalence of hepatitis B in inflammatory bowel disease, these patients are at risk of reactivation of Hepatitis B specially those who are taking Immunosuppresion. Earlier studies showed significantly higher prevalence than the general population(181).This high prevalence was due to surgical procedures and

blood transfusions which suggest nosocomial infection. Other studies have reported HBV infection rates in IBD patients which are similar to the general population(182)(183). Newer studies showed no differences in prevalence of Hepatitis B between CD and UC. However, in some studies, the prevalence of HBV markers was higher in CD than in UC (167).

Screening for Hepatitis B in inflammatory bowel disease

All the patients should be screened at diagnosis of inflammatory bowel disease. Waiting should not be done for initiation of immunosuppressive therapy(184)(9)(185).

Immunosuppresion effects on HBV infection:

Reactivation manifestations can vary such as change in serum liver enzyme levels to fulminant hepatic failure and death after taking Immunosuppresion. Hepatitis B reactivation is a well known complication after chemotherapy.Multiple studies has shown reactivation of hepatitis B after Anti-TNF therapy(6)(186)(187)(188).

Natural history of Hepatitis B in inflmamtory bowel disease:

Development for cirrhosis in HBV-infected IBD patients is reported to be same as in general population with HBV infection. Immunosuppresion in IBD, does not increase the risk of progression to end-stage liver disease in contrast to HCV-infected patients who progress to liver cirrhosis and hepatocellular carcinoma after liver transplantation(189).

Anti-viral prophylaxis:

(EASL), (AASLD),and(ECCO) advise early introduction of nucleotide/nucleoside analogues for HBsAg-positive patients who will require immunosuppressive therapy(13) (190). In patients who are positive HBsAg titres with or without viral replication; anti-viral therapy should be administered. Prophylaxis is given irrespective of the type and number of immunosuppressants administered(184). In IBD patients, it is recommended to start anti-viral prophylaxis 1–3 weeks prior to the initiation of immunosuppressive therapy and to continue therapy for six months after withdrawal(6)(190).

Occult Hepatitis B:

Is defined as persistence of B virus genome in HBsAg-negative individuals(191). Occult infection is common in patients who are positive for anti-HBc with or without anti-HBs. An AASLD guideline recommends screening for anti-HBc to detect occult HBV(184)(192). There are only few reports of HBV reactivation in an anti-HBc-positive/HBsAg-negative patient with CD treated with Immunosuppresion (193). Use of anti-viral prophylaxis in anti-HBc positive patients those who lack HBsAg cannot be recommended(194)(195). Prevalence of anti-HBc in voluntary blood donors is estimated to be 16% (196).

Anti-viral prophylaxis:

In chronic HBsAg-positive carriers, anti-viral prophylaxis is recommended before initiating immunosuppressive agents.(13) According to guidelines for HBV treatment; patients with high HBV DNA levels (>2000 IU/mL) should continue anti-viral therapy until endpoints like for any

other patient with hepatitis B are reached(197)(13). If immunosuppressive therapy is going to continue for more than one year, nucleotide/nucleoside analogues with a lower risk for generating drug-resistant mutations of HBV DNA should be preferred.

Hepatitis B vaccination in inflammatory bowel disease:

Vaccination prevents opportunistic infection IBD patients (8). In the course of IBD, patients may need immunosuppressive therapy. Response rates to vaccines, for example HBV vaccine seems to be lower in patients on immunosuppressive therapy (198). The time point of diagnosis of inflammatory bowel disease is the best time to vaccinate. Vaccine-related immunity duration appears to altered in patients with IBD with or without Immunosuppresion; so modified dosing schedules or booster doses would be necessary(199).Routine testing for immunity is not recommended after vaccination of adult, however testing is recommended for high-risk individuals such IBD patients(197)(179). An anti-HBs concentration of ≥10 mIU/mL measured one to three months after last dose of vaccination is considered a reliable marker of efficacy against infection according to the WHO (179)(200)(180).Those with anti-HBs concentrations <10 mIU/mL should be revaccinated with three additional doses(179)(201).There is a limited date available regarding the duration of immunological memory after Hepatitis B vaccination in immunocompromised patients. Immunocompromised patients should be tested annually to assess anti-HBs concentrations as in haemodialysis patients(202) as they are shown to have Hepatitis B infection after vaccination . Booster dose can be administered when anti-HBs levels decreases to <10 mIU/mL(202). Testing anti-HBs concentrations annually and administering booster doses when anti-HBs levels decreases to <10 mIU/mL) should be considered for IBD patients on

immunosuppressive treatment however more studies are required to establish this recommendation.

METHDOLOGY:

The study was designed as prospective case study analyzing the serological markers of Hepatitis B in patients with inflammatory bowel disease (IBD). It was presented to the Institutional Review Board & Ethics Committee, Christian Medical College, and Vellore and subsequently approved by the same. Patients with IBD were recruited between October 2013 and August 2014. Informed consent was taken from the patients themselves or their guardians (in case of children). Relevant data were collected through direct interviews with patients or guardians (in case of children) in the outpatient clinic as well in the wards when admitted.

HBsAg, a Hepatitis B marker was sent for all the recruited patients and in addition Anti-HBc was sent if HBsAg was found negative. Any patient found positive for serological markers of Hepatitis B was referred to department of Hepatology for further evaluation and management. Other investigations studied included Anti HCV & HIV status, liver function tests, imaging for evidence for chronic liver disease. Those positive for HBsAg were additionally tested for HBV DNA level and e Antigen status.

Demographic details, clinical, endoscopic and radiological details regarding inflammatory bowel diseases were entered into the proformas (Annexure 1). A detailed questionnaire was utilized to assess the risk factors for Hepatitis B transmission and vaccination status for hepatitis B.

Sample size:

The sample size for this study was calculated to be 76 based on 20% prevalence of Anti HBc in the general population, confidence level of 0.95 and precision level of 9%.

Statistical analysis:

The results were analyzed using SPSS version 15. Mean, median, standard deviation (SD), range, and proportions were calculated as appropriate. Categorical variables were analyzed using the Chi-square test with Yates' correction as applicable while continuous data was analyzed using Mann–Whitney U test. A 'p' value less than 0.05 was considered statistically significant.

Participants:

Inclusion criteria: All the patients with diagnosis of inflammatory bowel disease which included

1) Ulcerative colitis

2) Crohn's disease

3) Indeterminate colitis

Exclusion criteria: Patients (or parents/guardians in case of minors or incompetent patients) unwilling to give informed consent.

Definitions:

Ulcerative colitis: Chronic inflammatory condition causing mucosal inflammation in continuous segments of the colon without granulomas on biopsy, involving the rectum and a variable extent of the colon and characterized by a relapsing and remitting course.

Crohn's disease: Chronic inflammatory disorder involving any part of the alimentary tract from mouth to anus but with a propensity for the distal small intestine and proximal large bowel, inflammation being discontinuous along the longitudinal axis of the intestine with possible involvement of all layers of the gut wall from mucosa to serosa.

Indeterminate colitis: Chronic inflammatory bowel disease where biopsies show no equivocal features to suggest ulcerative colitis or crohn's disease are labeled as indeterminate colitis or colitis unspecified.

Serological markers of hepatitis B:

Hepatitis B surface antigen (HBsAg): Hallmark of HBV infection, usually detected by radioimmunoassay (RIA) or enzyme immunoassays (EIA).

Anti-HBc: It can be detected in three situations:

1) Window period of acute hepatitis B where the anti-HBc is mainly IgM class

2) After recovery from acute hepatitis B when anti-HBs decrease to the extent that it cannot be detected.

3) After many years of chronic HBV infection when HBsAg titer decreases below the cutoff for detection.

Present and past HBV infection was defined according to the terminology adopted by the National Institutes of Health conferences on Management of Hepatitis B (197). Present HBV infection included chronic hepatitis B and inactive HBsAg carrier state and past HBV infection included resolved hepatitis B (presence of anti-HBc with or without anti-HBs).

Variables:

Broad groups of variables included

1. Basic demographic details

2. IBD related history
3. Risk factors for hepatitis B transmission
4. Other clinical details
5. Investigations
6. Hepatitis B immunization details

Results:

A total 76 patients with inflammatory bowel disease were recruited for the study. Of the 76 patients, 42(55.3%) patients had diagnosis of ulcerative colitis, 33(43.4%) patients had diagnosis of Crohn's disease while only one patient had indeterminate colitis. The overall mean age for the entire study population was 37.5±13.9 years. Majority of the patients were from the following states: West Bengal: 25(32.9%); Tamil Nadu:16(21.2%); Jharkhand:13(17.1%); Andhra Pradesh:8(10.5%). The overall male: female ratio was 1.7:1 (48:28). 44(58%) of the patients were from an urban background. The overall median total duration of illness at the time of inclusion of the study was 35(1-410) months while the overall median duration prior to diagnosis of illness was 7.5(1-228) months. Table 1 depicts the baseline characteristics of the study patients with IBD.

Figure No.1: Diagnosis in inflmamtory bowel disease patients

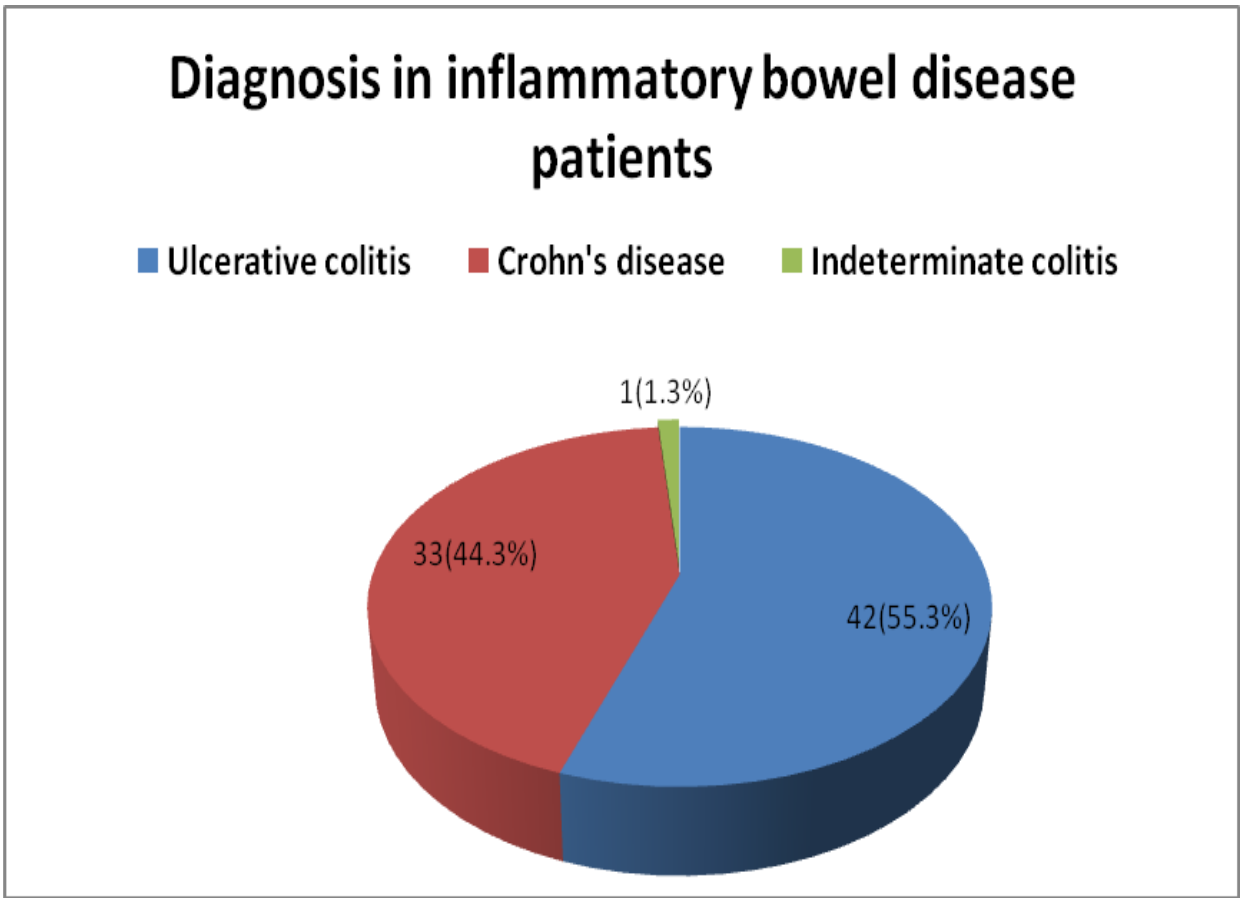


Figure.2: Sex distribution of Ulcerative colitis patients

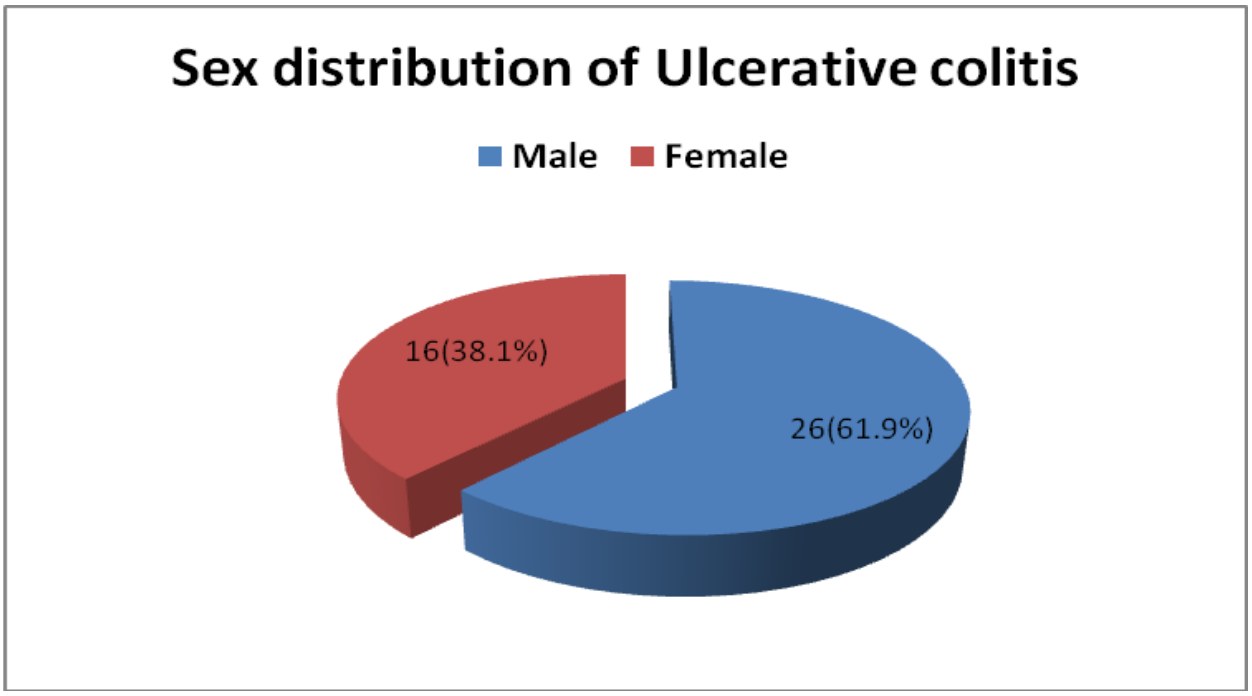


Figure.3:Sex wise distribution of Crohn's disease patients

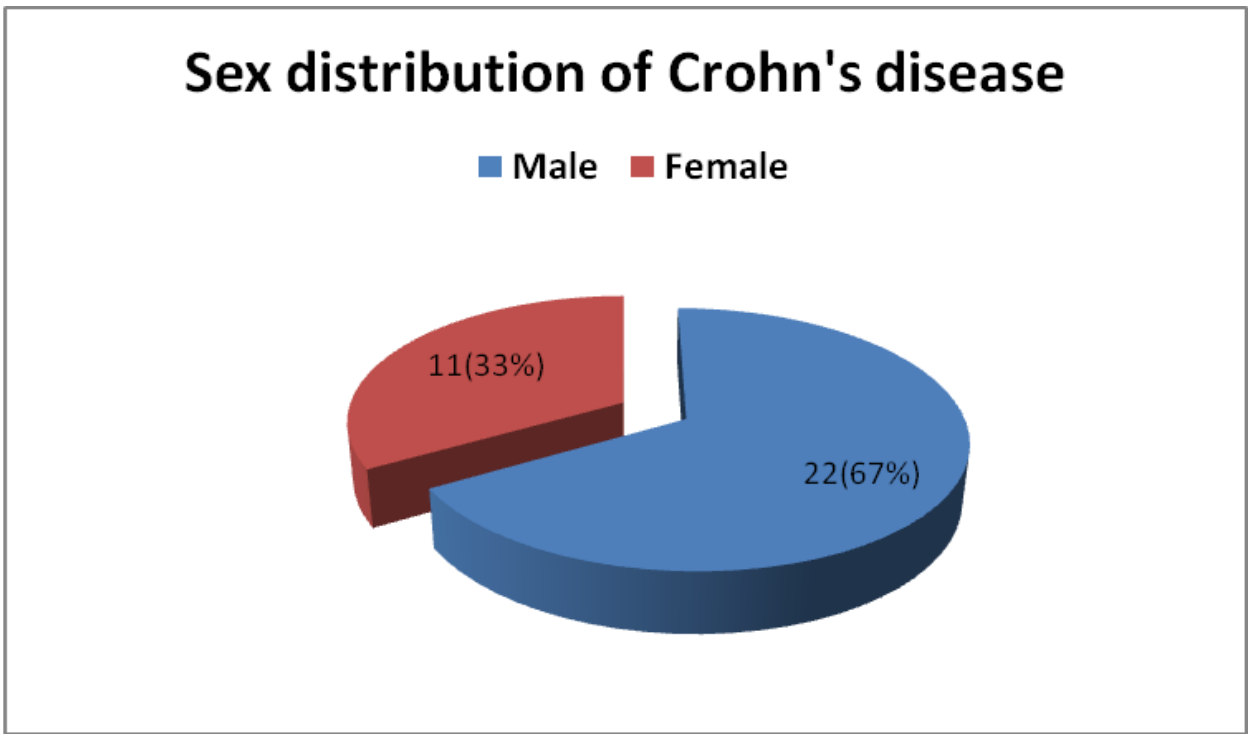


Figure.4: State wise distribution of cases

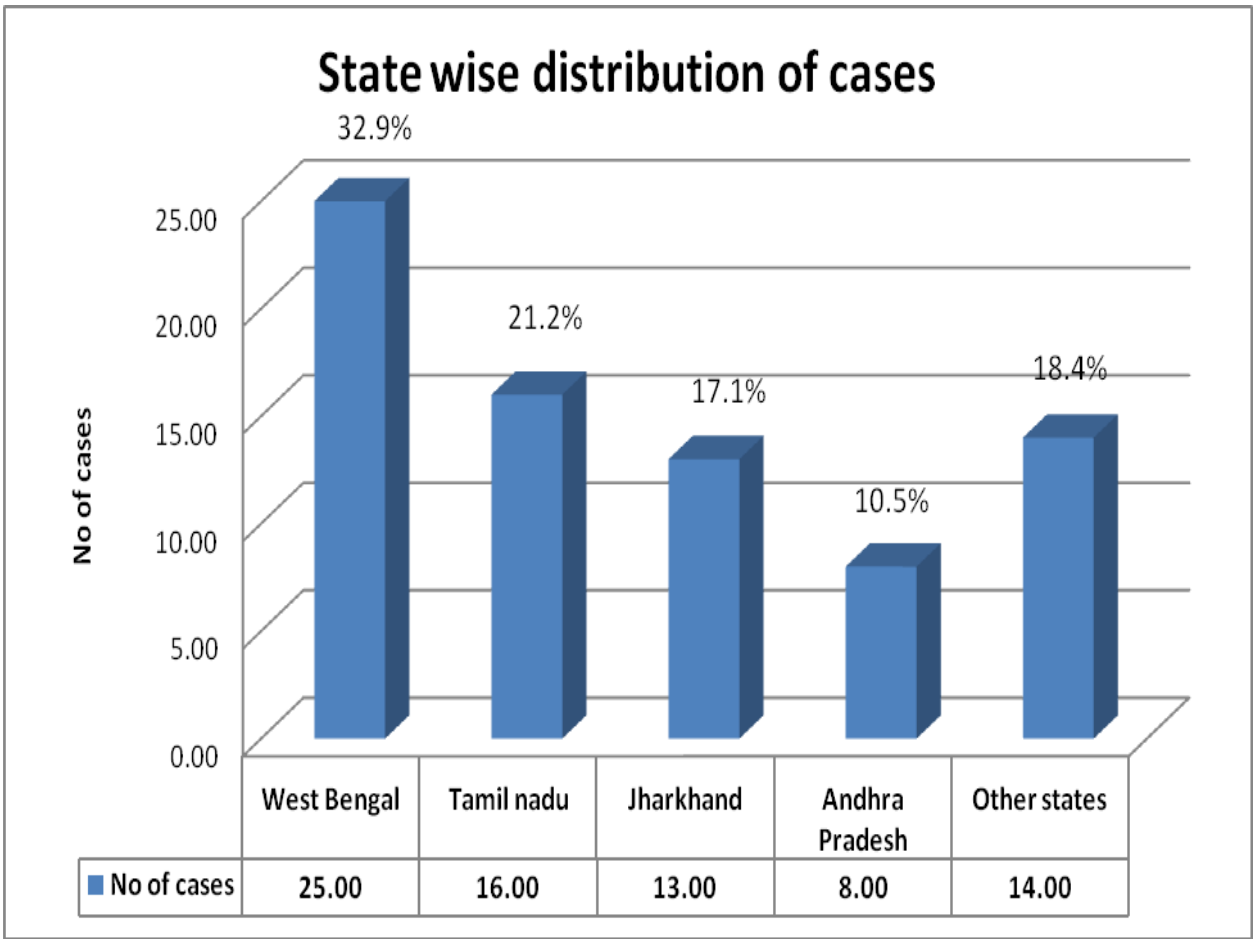


Figure.5: Regional distribution of cases

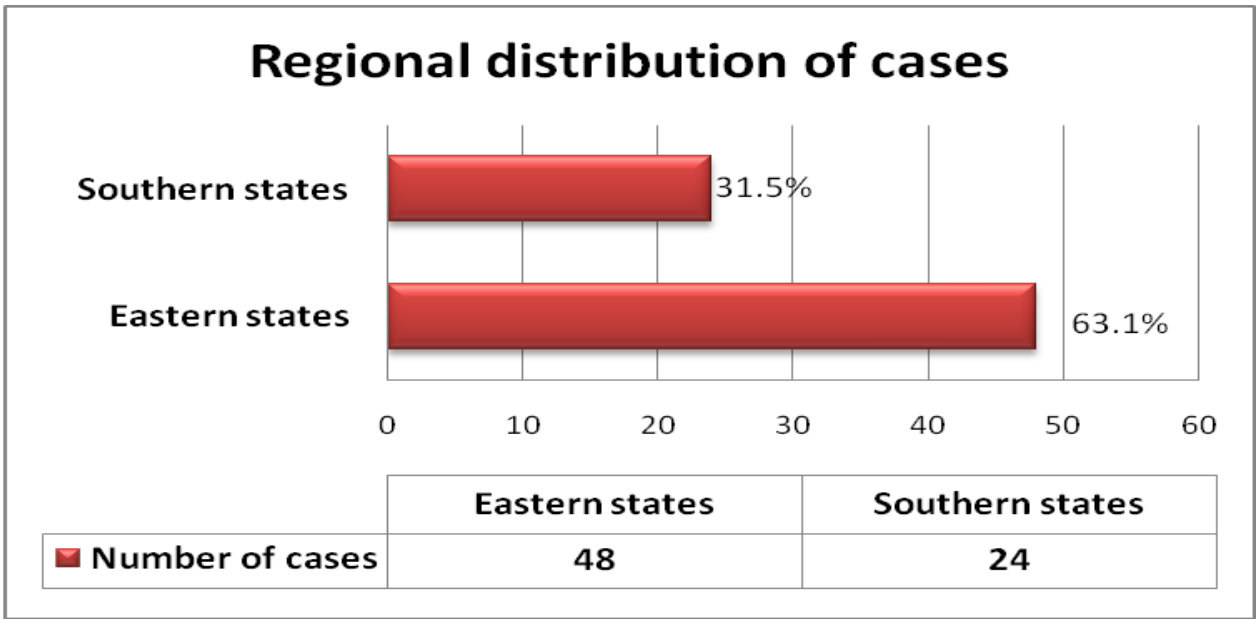
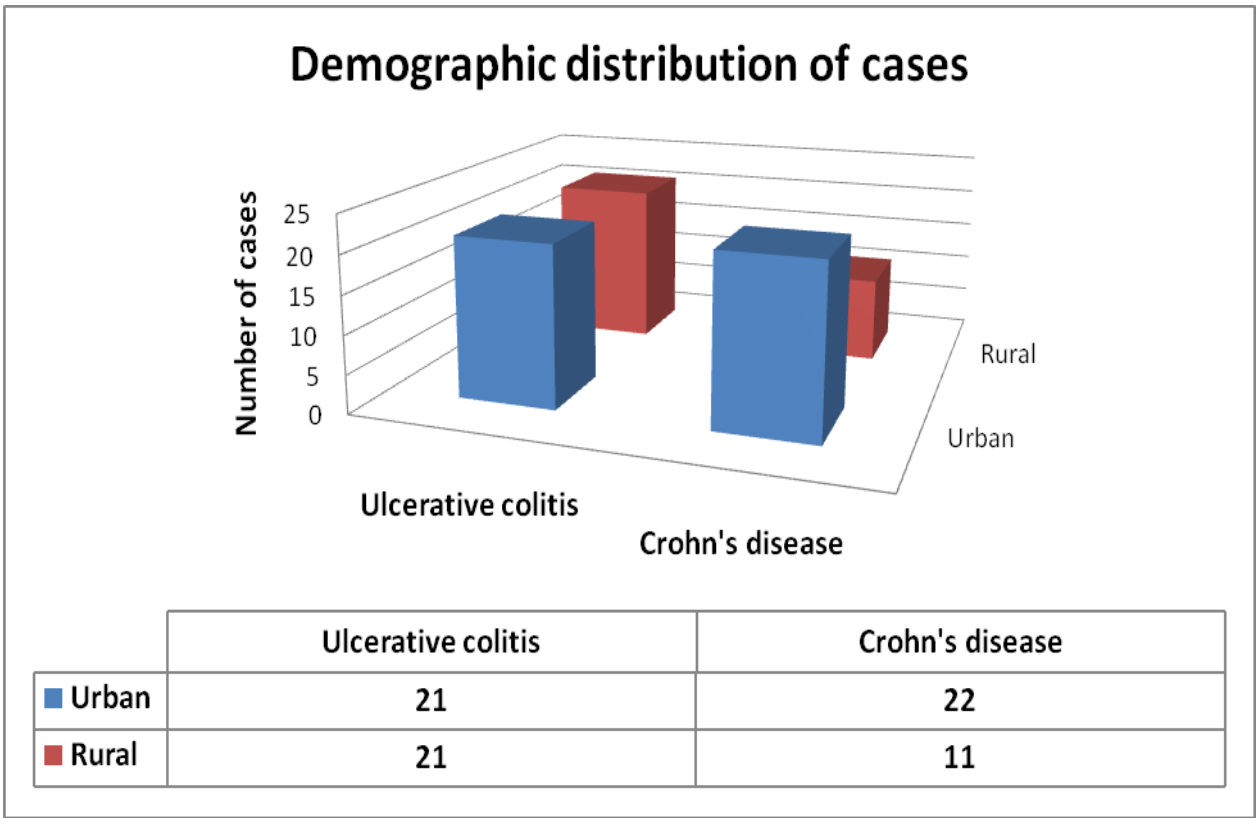


Figure.6:Demographic distribution of cases



Disease characteristics and related factors:

The mean ages of diagnosis for those with ulcerative colitis and Crohn's disease were 39.8±12.9 years and 34.3±14.7 years respectively. The Montreal classification was utilized to phenotypically classify patients with ulcerative colitis and Crohn's disease. Among patients with ulcerative colitis, 7 (16.7%), 15(35.7%) and 20(47.6%) patients had proctitis, left sided colitis and pancolitis respectively.

Among those with Crohn's disease; 7(21.2%), 20(60.6%) and 6(18.2%) patients were below 16, between 16 and 40 and more than 40 years respectively. 10(30.30%), 4(12.12%), 19(57.57%) and 0 (0%) had ileal, ileocolonic, colonic and upper gastrointestinal involvement. The nature of Crohn's disease was non-stricturing & non-penetrating, stricturing and fistulising in 14(42.4%), 14(42.4%) and 5(15.2%) respectively.

History of IBD related surgery was present in 2(4.8%) patients with ulcerative colitis and 8(24.2%) patients with Crohn's disease. In those with ulcerative colitis, both patients had history of surgery for anal fistula while in those with Crohn's, 3(9.1%) had small bowel resection, 3(9.1%) had right hemicolectomy while 2(6.1%) had surgery for anal fistula.

Although use of most medications like mesalamine, azathiporine, methotrexate and antibiotics were almost similar in both ulcerative colitis and Crohn's patients, the former (66.7%) had significantly more steroid intake than the latter (30.3%).

Figure.7: Medical therapy in patients of inflammatory bowel disease.

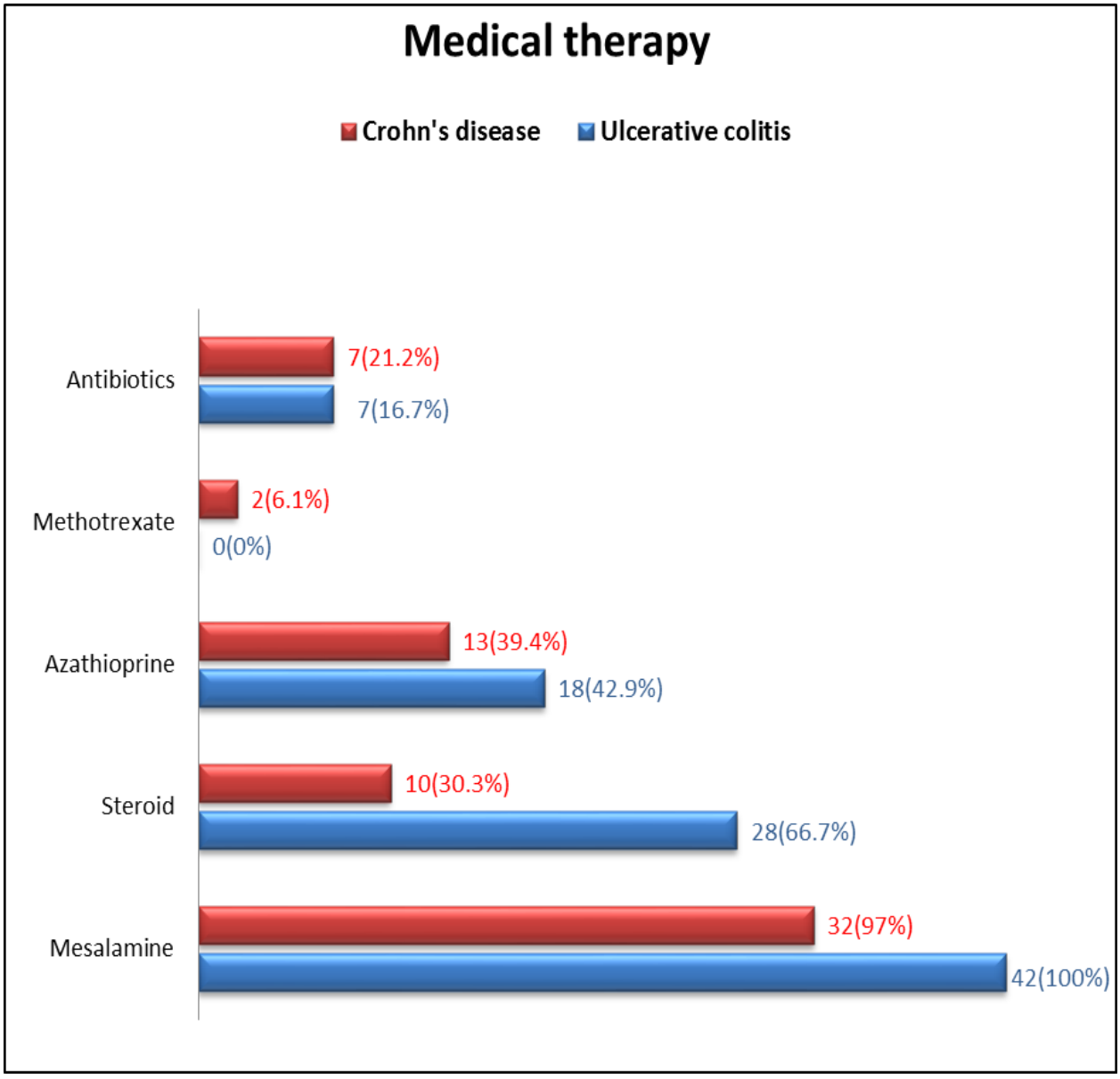
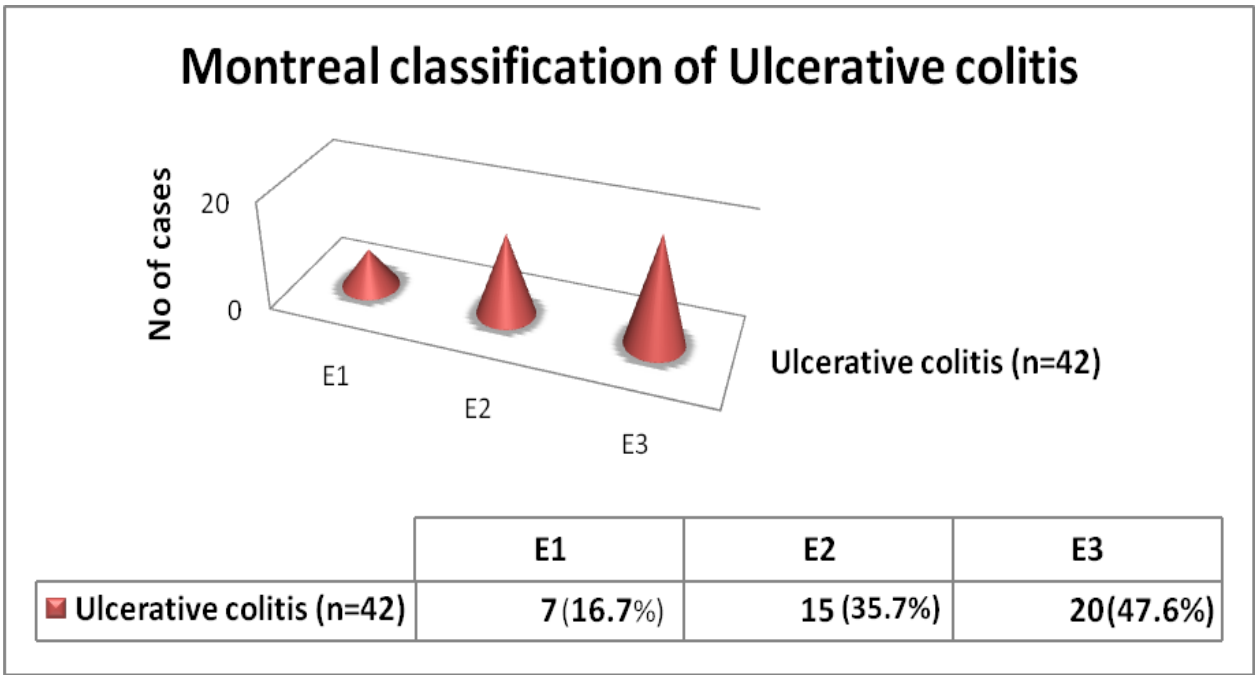


Figure.8: Montreal classification of Ulcerative colitis



	E1	E2	E3
Ulcerative colitis (n=42)	7 (16.7%)	15 (35.7%)	20(47.6%)

Figure.9:Montreal classfication of Crohn's disease according to age

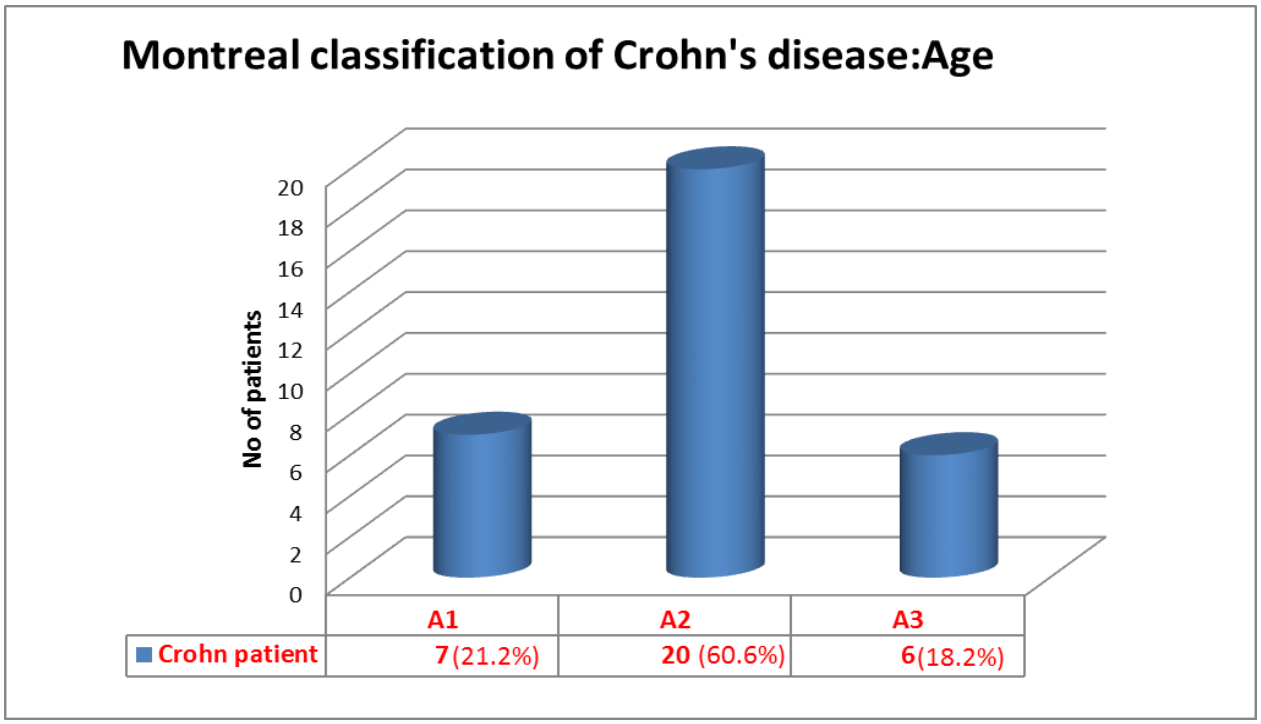


Figure.10: Montreal classification of Crohn's disease according to location

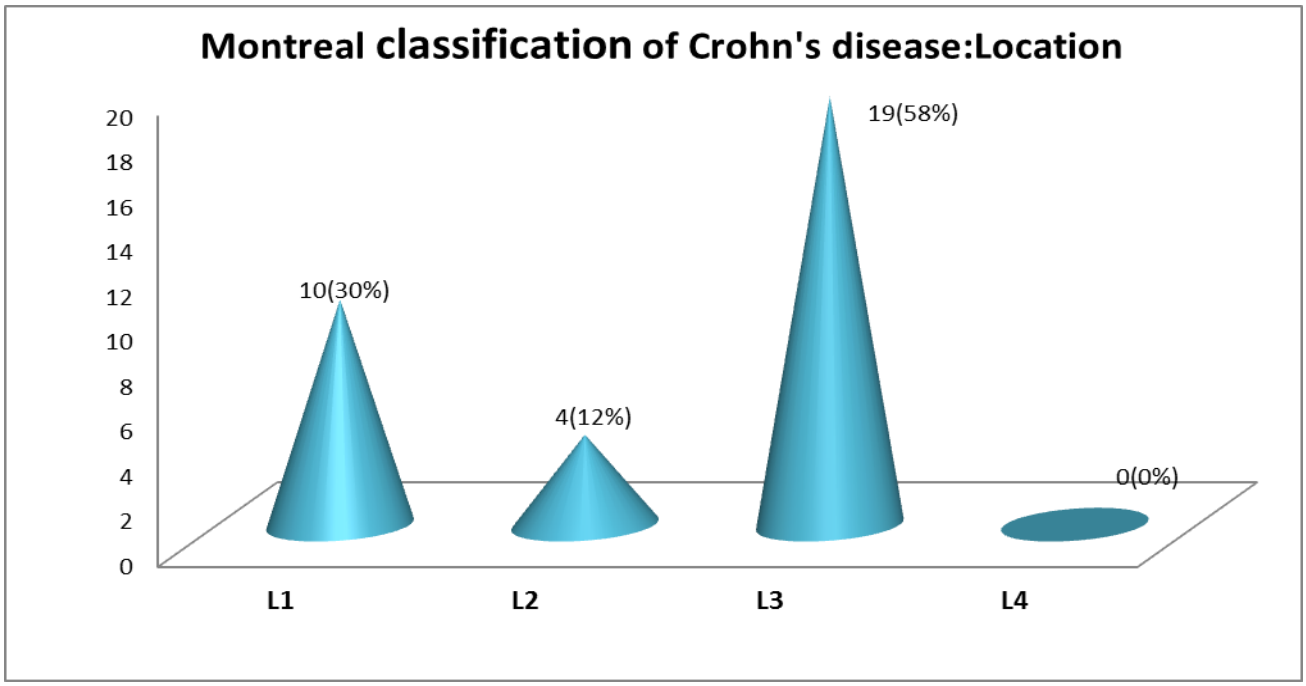


Figure.11:Montreal classfication of Crohn's disease according to behavior.

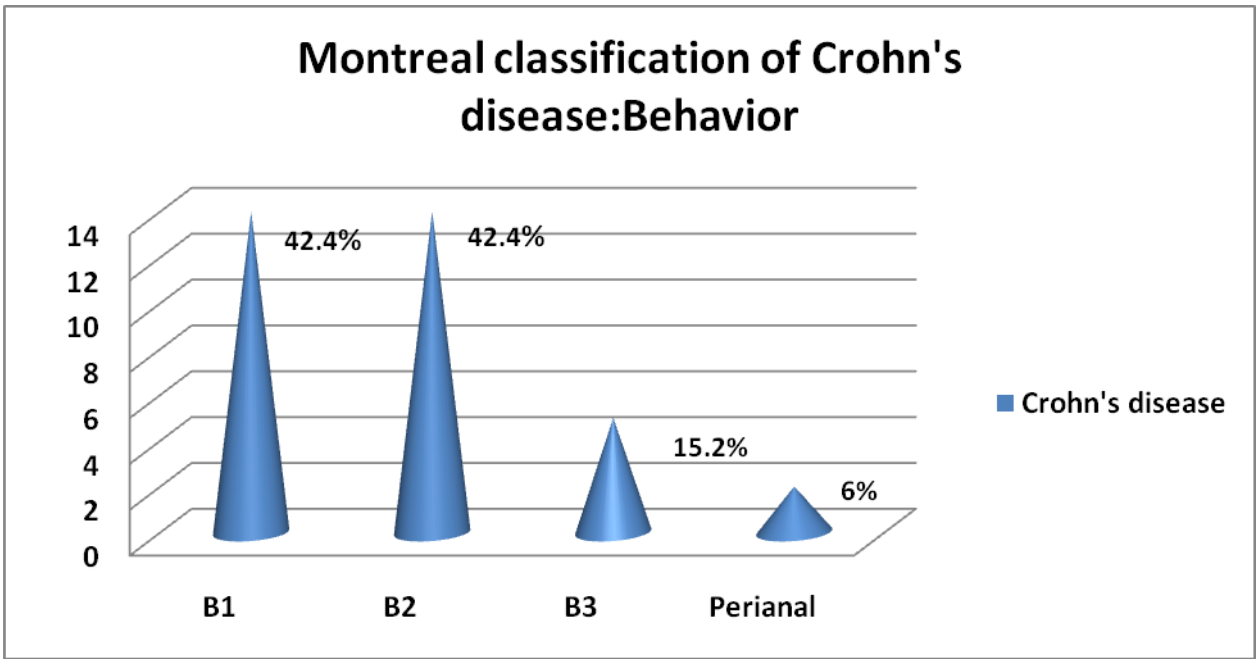


Table1: Baseline characteristic of study patients with IBD

	Ulcerative colitis (n=42)	**Crohn's disease (n=33)**	**Indeterminate colitis (n=1)**	**P value**
Mean age of diagnosis(SD)in years	39.8(12.9)	34.3(14.7)	48	0.092
Median total duration at inclusion (range) in months	27.5 (1-410)	36(2-328)	7	0.341
Duration prior to diagnosis(range) in months	6(1-80)	20(2-228)	5	0.004*
Male: Female	26(61.9%)/16(38.1%)	22(66.7%)/11(33.3 %)	0/1	0.809
Habitat: Urban /Rural	21(50.0%)/21(50.0%)	22(66.7%)/11(33.3 %)	1/0	0.166
Surgery related to IBD: Resection: Right hemicolectomy	0(0%) 0(0%)	1(3%) 3(9.1%)	0 0	

Medications :				
Mesalamine	42(100%)	32(97%)	1	0.44
Steroids	28(66.7%)	10(30.3%)	1	0.002*
Azathioprine	18(42.9%)	13(39.4%)	0	0.816
Methotrexate	0(0%)	2(6.1%)	1	0.19
Antibiotics	7(16.7%)	7(21.2%)	0	0.767
Montreal classification:	**Extension** E1: 7(16.7%) E2: 15(35.7%) E3: 20(47.6%)	**Age at diagnosis** A1: 7(21.2%) A2: 20(60.6%) A3: 6(18.2%) **Location** L1: 10(30.30%) L2: 4(12.12%) L3: 19(57.57%) L4: 0 (0%) **Behavior** B1: 14(42.42%) B2: 14(42.42%) B3: 5 (15.15%)		

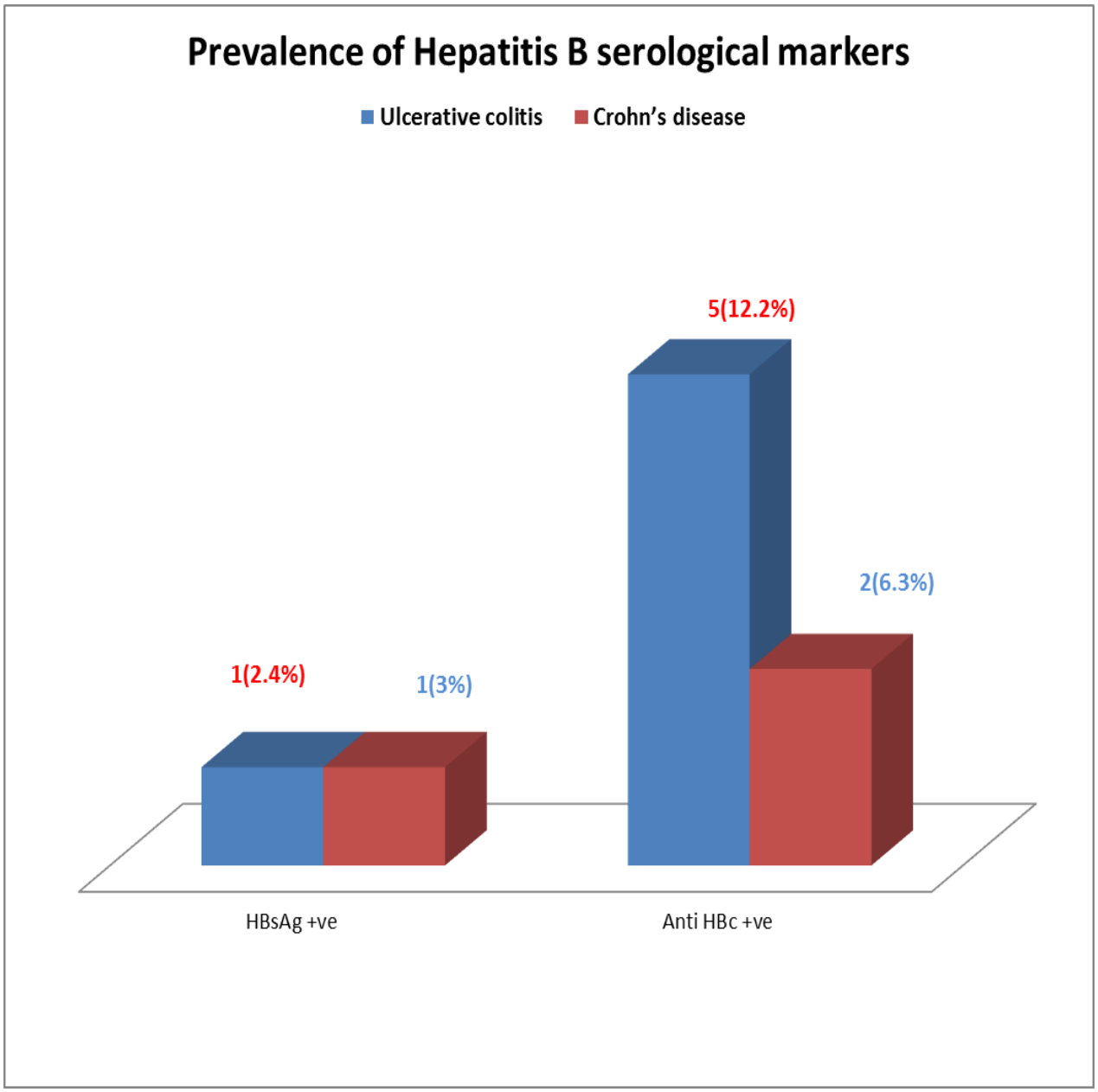
Prevalence of Hepatitis B markers in patients of inflammatory bowel disease

Hepatitis B markers (HBsAg/Anti-HBc) were positive in 9(11.8%, 95% CI: 6.4-21%) out of 76 patients with inflammatory bowel disease. None of the patients who were positive for hepatitis B markers had features of chronic liver disease or portal hypertension. Two patients who were positive for HBsAg were on anti-virals. Both the patients had low or negative viral levels. We had also tested for presence of hepatitis C virus which turned out to be negative for all the samples. Table 2 depicts the frequencies of hepatitis B markers in the study population.

Table 2: Prevalence of Hepatitis B markers in the study population

	Ulcerative colitis (N=42)	**Crohn's disease (N=33)**	**Indeterminate colitis (N=1)**
HBsAg +ve	1/42(2.4%)	1/33(3%)	0(0%)
Anti HBc +ve	5/41(12.2%)	2/32(6.3%)	0(0%)
HCV	0	0	0

Figure.12: Prevalence of Hepatitis B serological markers in cases



Factors related active or past Hepatitis B infection

Multiple risk factors were studied for active or past hepatitis B infection and compared between those who were positive and negative for hepatitis B related viral markers (Table 3). Out of the multiple risk factors studied mean age (P=0.034), non IBD related surgeries (P=0.009) and non IBD related hospital admission (P=0.008) were significantly more common in those positive for viral markers compared who were not.

Table 3: Risk factors related to active or past hepatitis B infection

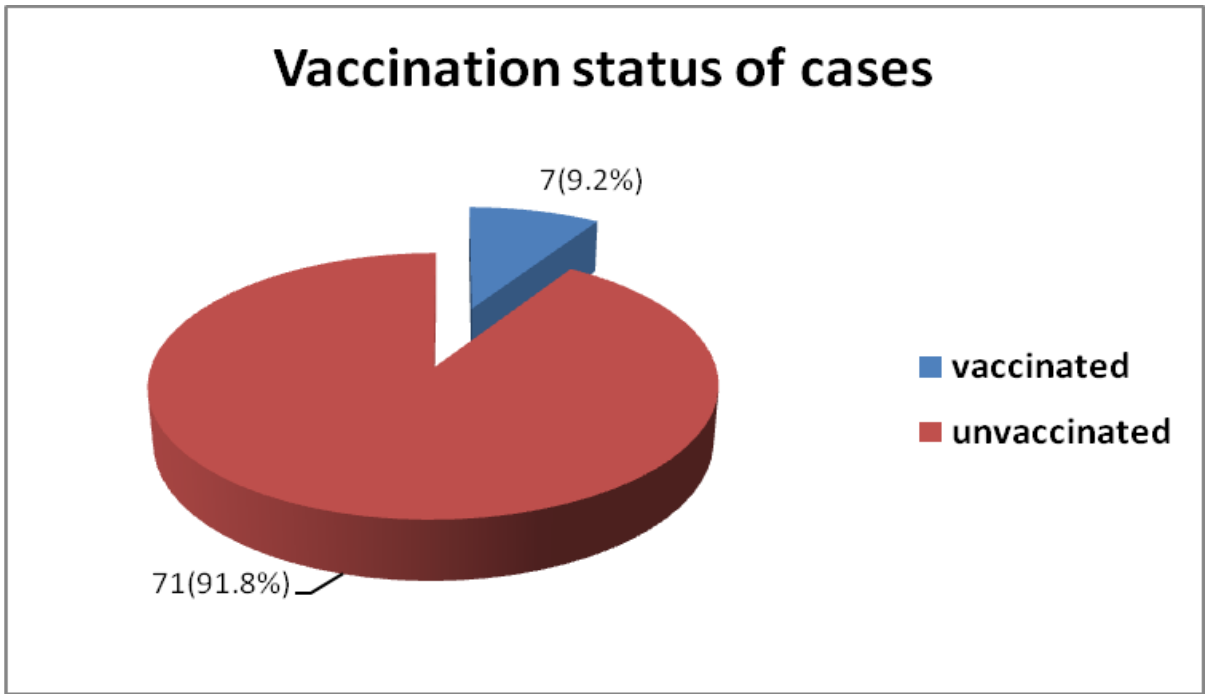
	Negative viral markers (n=67)	**Positive viral markers (n=9)**	**P value**
Mean age(SD)	36.3(13.9)	46.7(10.2)	0.034*
Male gender	43(64.2%)	5(55.6%)	0.718
Alcohol	4(6%)	2(22.2%)	0.146
Habitat (Urban)	36(53.7%)	8(88.9%)	0.071
Parenteral drug abuse	0(0%)	1(11.1%)	0.118
Parenteral injections	66(98.5%)	9(100%)	1
Dental	14(20.9%)	0(0%)	0.197
Family history	0	0	-
Maternal history	0	0	-
Surgeries (IBD)	10(14.9)	0	0.597
Surgeries (Non-IBD)	9(13.4%)	5(55.6%)	0.009*

Transfusions	14(20.9%)	2(22.2%)	1
Previous invasive procedures	56(83.6%)	6(66.7%)	0.354
High risk sex	1(1.5%)	0	1
Admission (IBD related)	28(41.8%)	4(44.4%)	1
Admission (non- IBD related)	14(20.9%)	6(66.7%)	0.008*
Hepatitis B in partner	0	0	
Steroids	35(52.2%)	4(44.4%)	0.733
Azathioprine	30(44.8%)	1(11.1%)	0.074
Methotrexate	3(4.5%)	0(0%)	1
Sharing towels	3(4.5%)	2(22.2%)	0.104
Health care worker	2(3%)	0	1
Tattooing	1(1.5%)	0	1
Piercing	21(31.3%)	4(44.4%)	0.465

Hepatitis B vaccination status

Out of 76 patients studied, only 7(9.2%) patients had completed 3 doses of vaccination. Out of these 7 patients, 6 were negative for hepatitis B markers while one patient tested positive for Anti-HBc.

Figure.13: Vaccination status of cases



Discussion:

Most available studies in published literature on the prevalence of hepatitis B serological markers in inflammatory bowel disease are from Western countries. (183)(182)(109)(203) Although there are three studies from East Asia , there are none from the Indian subcontinent (204)(205)(206). Prevalence rates of chronic hepatitis B in the general population varies across regions across the world with India falling under the intermediate prevalence category(207)(208). This study is the first one from India reporting the prevalence of hepatitis B infection among our patients with inflammatory bowel disease. Besides this is the first Indian study to provide hepatitis B vaccination rate in this vulnerable population.

Compared to other studies, we had only 76 patients with IBD, of which 55.3% had ulcerative colitis while 43.4% had Crohn's disease. There was one patient with indeterminate colitis. The largest series of this kind was the Spanish multicentre study by Loras el at in which they had 2076 patients (44.7% with ulcerative colitis and 54.3% with Crohn's) over 1 year. Chevaux et al from France recruited 315 patients (20% ulcerative colitis and 80% Crohn's) over a 4 year period. Katsanos et al from Greece reported a single centre study on 482 patients (64% ulcerative colitis, 30% Crohn's & 6% indeterminate colitis). From the United States, Ben Musa et al had 500 patients (ulcerative colitis 41.2%, Crohn's 58.4%, indeterminate colitis 0.4%) in their 3 year single centre retrospective series. There were 176 patients (42% ulcerative colitis and 58% Crohn's disease) in the single centre, two year, prospective Brazilian series reported by Tolentino et al. The largest Asian series was a 12 year, single centre retrospective series from China conducted by Huang et al in which they had 714 patients (44.4% ulcerative colitis, 55.6% Crohn's). Kim et al from Korea recruited 513 patients (53% ulcerative colitis and 47% Crohn's)

in their prospective, 3 year multicentre study. Leung et al had 267 patients (62.2% ulcerative colitis and 37.8% Crohn's) in their centre located at Hong Kong. Like most series, ours was a single centre study carried out over a year. The funds available for the study provided by the institutional fluid grant were taken into consideration while calculating our sample size We had more number of ulcerative colitis than Crohn's in our study similar to the pattern reported in our country's national survey of inflammatory bowel disease(209).

It is recommended that all IBD patients be screened for hepatitis B markers to rule the presence of hepatitis B infection and the optimal time for screening would be at the time of diagnosis(190).

In our study, male patients (66.7%) outnumbered their female counterparts (33.3%). The male: female ratio favoured the former even in the Indian survey (1.4 in ulcerative colitis and 1.3 in Crohn's(209). Male predominance was also seen in most studies(206)(204)(205)(210) However, the series from US, Brazil and Italy had more female patients(211)(109)(203) . In the series from Loras et al from Spain, male: female ratio was nearly one(173). Chevaux et al reported a male: female ratio of 0.38 among those with Crohn's disease and 0.62 among those with ulcerative colitis (174).

Majority of our patients were from urban areas. This was possibly due to their better accessibility to tertiary level healthcare compared to rural patients. The referral pattern to our centre may explain the predominance of patients from eastern and southern India. The study by Ben Musa et al (Chicago, USA) was the only one in which there was mention about race and ethnicity. Majority of the patients were Caucasian while Hispanics formed 8% of those with ulcerative colitis and 4.8% of those with Crohn's(203).

The overall mean age of the patients in our study was 37.5±13.9 years. The mean age for ulcerative colitis patients was 39.8±12.9 years while it was 34.3±14.7 years for Crohn's patients. In the Indian survey of IBD, mean age of patients with ulcerative colitis and Crohn's were 38.5 (13.5) and 35.9 (13.9) years respectively(209). Most Western studies had older patients in their series(203)(182)(210)(109). However, Chevaux et al had younger patients in their study population where median (IQR) age was 33(24-43) years(183) .With regard to Asian studies; Huang et al from China had their overall mean age (37.25 +/- 9.83 years) similar to ours. Kim et al from Korea reported mean age of 29.89+/- 11.72 years from Crohn's and 43.97+/- 15.31 for their ulcerative colitis patients while Leung et al from Hong Kong reported figures of 42.2+/- 14 and 51.7+/-14.1 years respectively(204).

The overall median duration of illness at the time of inclusion in our study was 35(1-410) months; 27.5(1-410) months for ulcerative colitis and 36(2-328) months for Crohn's. The mean duration of illness was much longer in the series from Spain (100 months), US (134+/-127.6 months) and Italy (9.9 +/- 7.7 years)(182)(203)(109) .

Use of immunosuppressive drugs can exacerbate hepatitis B infection in those with IBD. Steroids, azathiporine and methotrexate was used in 38(50%), 31(40.8%), 2(2.6%) in our study population respectively. The steroid use was more significantly (p=0.002) seen in those with ulcerative colitis (66.7%) than Crohn's disease (30.3%). None of our patients had a history of biologic agents use in the treatment of IBD. Immunosuppressive and biologic agents were widely used in other studies. In the study by Tolentino *et al* 4% used immunosuppressant drugs, 42% used steroids and both the drugs were used in 26% patients(211). In the study by Chevaux et al, overall 68.9% (95% CI: 63–74) were treated with immunosuppressive agents including Anti TNFα agents. Azathioprine, methotrexate and Anti-TNFα agent use was seen in 52%, 4.8% and

52.4% patients with Crohn's and 31.7%, 15.9% and 27%, patients with ulcerative colitis respectively(183). Loras et al reported 79% of their patients were treated with immunosuppressive therapy while Ben Musa et al reported a figure of 60%(182)(203). The largest series for China by Huang et al reported that 23% had immunosuppressive therapy while 8.5% received Infliximab. Kim et al from Korea reported that steroids, thiopurines and biological were used in 49.8%, 53.1%, 13.7% of Crohn's and 46%, 23.2 %, 2.6% of ulcerative colitis patients respectively(204). In study by Leung et al from Hong Kong; steroids, thiopurines and biological were used in 22.8%, 49.5%, 14.95% of Crohn's and 13.9%, 10.8%, 1% of ulcerative colitis patients respectively(205). Steroids and immunosuppressant can cause reactivation of latent hepatitis B virus. Unlike cancer patients who are frequently exposed to cytotoxic chemotherapy and immunomodulators, there is a lack of awareness even among gastroenterologists that IBD patients are also vulnerable to reactivation of hepatitis B virus since they are also exposed to similar treatments(7).

There are several reports of reactivation of hepatitis B virus in IBD patients when exposed to steroids, thiopurines, anti TNF drugs. There is also increased level of reactivation in patients when administered a combination of these drugs(10).

There is increased risk of death due to fulminant liver failure after administration of chemotherapy in 4 to 60% cases. In patients with IBD who are HBs Ag positive, it would be important to cover them with antivirals during their course of steroids, immunomodulators and biologic agents. Tenofovir and Entecavir are preferred to lamivudine for antiviral prophylaxis(10) The strategy for management of HBs Ag-ve but Anti HBc +ve patients is a matter of debate. The ECCO guideline recommends that routine antiviral prophylaxis is not recommended. However it advises to monitor LFT, HBV serology and viral loads. NIH (2009)

consensus advocates anti-viral prophylaxis for those patients planned for organ or bone marrow transplantation or if aggressive or prolonged chemotherapy is considered.

In our study13.2% patients had IBD related surgery while 18.5% had non- IBD related surgery. Loras et al from Spain reported 28% of their patients had IBD related surgery while Chevaux et al from France reported a figure of 33.7% (95% CI: 28–39). In the latter series; 21%, 11.5% & 14.3% of Crohn's patients underwent ileal resection, colectomy and perianal surgery while 7.94% patients underwent colectomy for ulcerative colitis(183)(182). From Hong Kong study, Leung et al reported that 33.7% and 18% patients of Crohn's and ulcerative colitis respectively had previous history of bowel resection(205). Huang et al from China had 22% who underwent IBD related surgery while Kim et al (Korea) reported a figure of 17.3%(204)(206).Papa et al from Italy reported that 53.2% had previous history of surgery(109). The highest figure for past history of surgery was 66.5% reported by Tolentino et al from Brazil(211). Compared to other series, history for IBD related surgery was least in our study group. Like Tolentino et al, we had more non-IBD related surgery than IBD related surgery. Other than the Brazilian and Chinese series; most series did not provide data on non-IBD related surgeries.

According to Montreal classification in ulcerative colitis pancolitis (47.6%) was the commonest presentation in our study. In those with Crohn's disease, commonest age group was A2 i.e., between 17-40 years (60.6%); ileocolonic(57.6%) was the commonest location while B1(inflammatory) and B2(stricturing) were most common type of disease behavior, both being 42.4%.These results were similar to that reported by Loras et al where pancolitis (41.7%) was the commonest presentation in ulcerative colitis while A2(68.6%), ileocolonic location(41.3%) and B1 (46.5%) were the commonest presentation seen in Crohn's(182). In contrast in the study by

Chevaux et al; B3 i.e. penetrating (41.7%) was the commonest behavior in Crohn's disease(183). The Asian studies had similar clinical presentations to ours with respect to both Crohn's and Ulcerative colitis except that isolated proctitis was the most common extent of UC in the series from China and Korea(206)(204).

In our study, the overall prevalence for serological markers of hepatitis B infection was 11.8%; HBs Ag was present in 2.6% while anti HBc was seen in 9.5% of those tested. More patients with ulcerative colitis (12.2%) were anti HBc positive compared to those with Crohn's (6.3%) although not significantly. The prevalence of hepatitis B markers (11.8%) was not significantly different from the available figure in the general population (20.3%) (212).

On comparison with other studies, Katsanos et al from Greece & Chevaux et al from France reported the least (2.3% & 2.54% respectively) figures for seroprevalence of hepatitis B markers. This was closely followed by Ben Musa et al from US (3.6%). The highest prevalence rates were reported from China (Huang et al, 40.62%) followed by Korea (Kim et al, 30%). From Brazil, Tolentino et al reported seroprevalence of 17%(206)(204).

The highest overall prevalence of HBsAg among IBD patients were from all from Asian studies: Leung et al (6.7%), Huang et al (5.46%) & Kim et al (3.7%). The highest overall prevalence of anti HBc among IBD patients were again from Asia: Huang et al(40.62%), Kim et al (30%) & Leung et al(28.5%)(206)(204)(205).

.Except for the studies from US (Ben Musa et al) and France (Chevaux et al), the prevalence of anti HBc in ulcerative colitis exceeded the prevalence seen in Crohn's disease(203)(183).

The variations in seroprevalence of hepatitis B in IBD patients across the above mentioned could be possibility explained by the differences in the local prevalence of hepatitis B, regional differences in the same country, vaccination policies & implementation and the age of the study subjects(183). Understandably, higher figures of seroprevalence were obtained in studies reported from Southeast Asia and Brazil while the lowest were reported from Europe. Italian data showed that even in the same country; adoption of important public health measures like improved screening of blood and blood products, universal precautions in health care settings and effective implementation of hepatitis B vaccination programs could result in reduced rates of seroprevalence over a period of time(109). Our data from India would suggest that our country stands somewhere in the middle not only in terms of prevalence but also with regard to successful implantation of crucial public health measures.

On analyzing the risk factors associated with hepatitis B infection in IBD patients, older age was commonly noted in the available studies including ours(182)(211)(206). The other significant risk factors obtained in the study from Spain were family history of hepatitis B infection and presence of moderate-severe IBD(182). In the study from China from Huang et al, family history of hepatitis B and IBD related admissions were the other significant risk factors(206). In our study, history of non-IBD admissions and non-IBD surgeries were noted to be significantly associated with risk for hepatitis B infection.

An older age is associated with longer disease duration of IBD which increases the risk of contracting hepatitis B infection(211) Family history of hepatitis B infection indicates the increased risk for viral transmission among household contacts (eg: sharing of razors & toothbrushes) and also through sexual contact. Vertical transmission from infected mother to fetus is an important route of transfer in developing countries. Moderate – severe IBD may lead

to increasing need for IBD related admissions, parenteral injections and surgeries. Interestingly in our study, the significant association between non-IBD related admissions/surgeries and hepatitis B infection could indicate that these are opportunities for transmission of the virus. Improper sterilization and reuse of sharp instruments, frequent and unwarranted parenteral injections, substandard blood banking facilities and lack of awareness of infection control in primary and secondary health care settings in India may contribute to increased risk for infection(213)(214).

Effective vaccination is generally defined as presence of anti HBs titres > 10 IU/ml without anti HBc positive(183). In the Spanish study, effective vaccination was seen in 12% of the patients; 12.9% in Crohn's and 11.1 % in ulcerative colitis. This study also noted that younger IBD patients were more significantly protected against hepatitis B infection compared to their older counterparts (56.5%vs 12.3%) suggesting that vaccine effectiveness decreases with age(182). The highest rate for effective vaccination was reported from France by Chevaux et al to be 48.9% (Crohn's 45.6% and ulcerative colitis 61.9%)(183). Papa et al from Greece reported a vaccination rate of 23.9%(109). From Asia; Kim et al from Korea reported effective vaccination of 38.1% (Crohn's 37.2% and ulcerative colitis 38.9%) while Leung et al reported a rate of 26.6% (Crohn's 24.7% and ulcerative colitis 27.7%)(204)(205). Huang et al from China reported an effective vaccination rate of 21.57%(206). Out of a total of 193 patients, Ben Musa et al in their retrospective series reported that (49%) were vaccinated(203). In our study, only 9.2% ever received 3 doses of hepatitis B vaccine. We did not check the anti HBs titres in these patients as part of the study.

Although the ECCO guidelines recommend hepatitis B vaccination in inflammatory bowel disease patients, it is underutilized(15). Unfortunately the awareness about the need for

hepatitis B vaccination particularly among physicians is low. In countries where universality of hepatitis vaccination is ensured, lower rates of hepatitis B seromarker prevalence were noted. The highest effective vaccination obtained in the French study maybe attributed to the country's vigorous vaccination program. Coverage of high risk groups for hepatitis B infection was started in 1981. By 1995, hepatitis B vaccine became part of the French national immunization schedule(183).

It is recommended that hepatitis B vaccination be administered at the time of diagnosis of IBD prior to the start of immunosuppressant (10)

Several factors have been identified for the poor or non response to hepatitis B vaccination in healthy subjects like immunosuppressive disease, older age, male sex, smoking and increased body mass index(10).Efficacy of vaccine in IBD patients may decrease with age shown in the Spanish study. Use of immunomodulators may also decrease vaccine effectiveness. Chaparro et al also noticed that patients on TNF agents had poor response rates(10). It is also felt that Crohn's per se could affect vaccine effectiveness by modulating Th1/Th2 balance which in turn may dysregulate cytokine production leading to diminished vaccine response(183). Not only should the full course of hepatitis B vaccination be given, it should be ensured that adequate titres are obtained. Those who have inadequate response may need a second course of hepatitis B vaccination. Despite initial failure, it is felt that 50% of those who take a second course may develop adequate antibody response to the vaccine(184).

Limitations of the study:

1) Single centre study
2) Being a major tertiary care centre in South India, a referral bias is expected in our study.
3) Smaller sample size

Conclusions:

1) The prevalence of serological markers of hepatitis B exposure in our study patients with inflammatory bowel disease patients was 11.8%.

2) An older age, history of non-IBD related admission and non-IBD related surgery were significantly associated with risk for hepatitis B infection.

3) Hepatitis B vaccination rate among our study population was very low (9.2%) indicating that it was grossly underutilized.

4) There is a need to create awareness among physicians regarding the need for hepatitis B vaccination in patients with inflammatory bowel disease.

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Proforma:

Serial No: **Date:**

PROFORMA (HEP B & IBD)

NAME: HOSPITAL NO:

AGE: SEX: 1. MALE 2. FEMALE

OCCUPATION:

POSTAL ADDRESS:

HABITAT: 1) URBAN 2) RURAL

PHONE NO: 1) 2)

EMAIL:

IBD RELATED HISTORY

DIAGNOSIS: 1) CROHN'S DISEASE 2) ULCERATIVE COLITIS 3) INDETERMINATE COLITIS

MONTH AND YEAR IN WHICH FIRST DIAGNOSIS WAS MADE:

DURATION OF ILLNESS PRIOR TO FIRST DIAGNOSIS (MONTHS):

TOTAL DURATION (MONTHS):

SITE OF INVOLVEMENT:

CROHN'S: 1) ILEAL (1.YES 2.NO) 2) COLONIC (1.YES 2.NO) 3) ILEOCOLONIC (1.YES 2.NO)

4) UPPER GI DISEASE (1.YES 2.NO) 5) PERIANAL (1.YES 2.NO)

UC: 1) PROCTITIS (1.YES 2.NO) 2) LEFT SIDED (1.YES 2.NO) 3) PANCOLITIS (1.YES 2.NO)

EXTRAINTESTINAL MANIFESTATIONS:

JOINT DISEASE - 1) AXIAL 2) PERIPHERAL 3) NOT INVOLVED

ORAL DISEASE- 1) YES 2) NO If YES, mention:

SKIN DISEASE- 1) YES 2) NO If YES, mention:

EYE DISEASE - 1) YES 2) NO If YES, mention:

LIVER DISEASE - 1) YES 2) NO If YES, mention:

BEHAVIOUR OF CD:

1. NON STRICTURING, NON FISTULISING

2. STRICTURING

3. FISTULISING Type:

COLORECTAL MALIGNANCY: 1) YES 2) NO

CURRENT DRUGS:

AMINOSALICYLIC ACID 1) YES 2) NO

STEROIDS 1) YES 2) ORAL / INTRAVENOUS

AZATHIOPRINE 1) YES 2) NO

METHOTREXATE 1) YES 2) NO

INFLIXIMAB 1) YES 2) NO

CYCLOSPORINE 1) YES 2) NO ORAL / INTRAVENOUS

ANTIBIOTICS 1) YES 2) NO ORAL / INTRAVENOUS

TYPE:

PAST HISTORY OF DRUGS:

AMINOSALICYLIC ACID 1) YES 2) NO DURATION (M)

STEROIDS 1) YES 2) NO ORAL / INTRAVENOUS NO. OF COURSES USED:

AZATHIOPRINE 1) YES 2) NO DURATION (M)

METHOTREXATE 1) YES 2) NO DURATION (M)

INFLIXIMAB 1) YES 2) NO DURATION (M)

CYCLOSPORINE 1) YES 2) NO DURATION (M) ORAL / INTRAVENOUS

ANTIBIOTICS 1) YES 2) NO DURATION (M) ORAL / INTRAVENOUS

TYPE:

SURGERY: 1) YES 2) NO IF YES, TYPE OF SURGERY _____

HISTORY OF ALTERNATIVE MEDICINE 1) YES 2) NO

1) AYURVEDIC 2) HOMEOPATHY 3) UNANI 4) OTHERS (MENTION)

RISK FACTORS FOR HBV TRANSMISSION

HISTORY OF PARENTERAL INJECTIONS: 1) YES 2) NO

PARENTERAL DRUG ABUSE: 1) YES 2) NO

HISTORY OF TRANSFUSIONS: 1) YES 2) NO PRODUCT USED & NO:

MATERNAL HISTORY OF HEPATITIS B: 1) YES 2) NO

DENTAL PROCEDURES: 1) YES 2) NO

BODY TATOOING: 1) YES 2) NO

HISTORY OF PIERCINGS: 1) YES 2) NO

SHARING OF BRUSHES/RAZORS/EARRINGS**:** 1) YES 2) NO ITEM:

SHARING OF TOWELS: 1) YES 2) NO

WHETHER PATIENT IS HEALTH CARE WORKER? 1) YES 2) NO

FAMILY HISTORY OF HEPATITIS B: 1) YES 2) NO

HISTORY OF HEPATITIS B IN PARTNER: 1) YES 2) NO

PREVIOUS IBD RELATED ADMISSIONS: 1) YES 2) NO

PREVIOUS NON-IBD RELATED ADMISSIONS: 1) YES 2) NO

HISTORY OF OTHER INVASIVE PROCEDURES (LIKE INTERVENTIONAL RADIOLOGY, INTUBATIONS, ENDOSCOPIES, TAPS, PUNCTURES, BIOPSIES): 1) YES 2) NO

DETAILS:

SURGERY UNRELATED TO IBD: 1) YES 2) NO

DETAILS:

HIGH RISK SEXUAL BEHAVIOUR 1) YES 2) NO

OTHER CLINICAL DETAILS:

ALCOHOL CONSUMPTION: 1) CURRENT 2) FORMER 3) NEVER

QUANTITY: UNITS/WEEK: YEARS:

HISTORY OF LIVER DISEASE- JAUNDICE/CLD/ DECOMPENSATION: 1) YES 2) NO

DETAILS:

PAST HISTORY OF DOCUMENTED HBV FLARE: 1) YES 2) NO

HISTORY OF ANTIVIRALS: 1) YES 2) NO

INVESTIGATIONS:

HBsAg: 1) POSITIVE 2) NEGATIVE Anti HCV: 1) POSITIVE 2) NEGATIVE

HIV: 1) POSITIVE 2) NEGATIVE Anti HBc (Total): 1) POSITIVE 2) NEGATIVE

HBeAg: 1) POSITIVE 2) NEGATIVE Anti-HBe: 1) POSITIVE 2) NEGATIVE

HBV DNA: 1) POSITIVE 2) NEGATIVE HBV viral load:

LFT (Total Bb/ Direct Bb / Prot /Alb / SGOT / SGPT / ALP):

INR:

ABD IMAGING

USG 1) YES 2)NO

CT 1) YES 2)NO

MRI 1) YES 2)NO

IMAGING FINDINGS:

CLD 1) YES 2) NO PHT 1) YES 2) NO HCC 1) YES 2) NO

HEPATITIS B IMMUNIZATION DETAILS

PRIOR HBV VACCINATION: 1)YES 2)NO 3)UNSURE

HOW MANY DOSES: 1/2/3

DURATION SINCE 3RD DOSE (M):

WHETHER EVER Anti-HBs CHECKED: 1) YES 2) NO

WHETHER Anti-HBs titer > 10 mIU/ml: 1) YES 2) NO

COUNSELLING : ADVISED IMMUNISATION 1) YES 2) NO

THREE DOSES RECEIVED 1) YES 2) NO